

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/18, 31/155, 31/445, 31/495, C07C 277/00, 279/00, 279/12, C07D 211/26, 211/60, 241/04, 295/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/11693</p> <p>(43) International Publication Date: 3 April 1997 (03.04.97)</p>
<p>(21) International Application Number: PCT/US96/15609</p> <p>(22) International Filing Date: 27 September 1996 (27.09.96)</p> <p>(30) Priority Data: 08/536,939 29 September 1995 (29.09.95) US 08/698,401 15 August 1996 (15.08.96) US</p> <p>(71) Applicant: 3-DIMENSIONAL PHARMACEUTICALS, INC. [US/US]; Eagleview Corporate Center, 665 Stockton Drive, Exton, PA 19341 (US).</p> <p>(72) Inventors: LU, Tianbao; 45 Surrey Way, Exton, PA 19341 (US). ILLIG, Carl, R.; 25 Jonathan Drive, Phoenixville, PA 19460 (US). TOMCZUK, Bruce, E.; 333 Sonnet Lane, Collegeville, PA 19426 (US). SOLL, Richard, M.; 324 Glenn Avenue, Lawrenceville, NJ 08648 (US). SUBASINGHE, Nalin, L.; 129 Longford Road, West Chester, PA 19380 (US). BONE, Roger, F.; 797 Garfield Avenue, Bridgewater, NJ 08807 (US).</p> <p>(74) Agents: GOLDSTEIN, Jorge, A. et al.; Sterne, Kessler, Goldstein & Fox P.L.L.C., Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: GUANIDINO PROTEASE INHIBITORS</p> <p>(57) Abstract</p> <p>Compounds of formula (I) wherein R¹-R⁴, R⁷-R⁸, R^a, R^b, R^c, Y, Z, n and m are set forth in the specification, as well as hydrates, solvates or pharmaceutically acceptable salts thereof, that inhibit a number of proteolytic enzymes are described. Also described are methods for preparing the compounds of Formula (I).</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

Guanidino Protease Inhibitors

5

Background of the Invention

Field of the Invention

The present invention relates to novel compounds that function as enzyme inhibitors, and particularly to a new class of non-peptidic inhibitors of proteolytic enzymes.

10

Related Art

15

20

25

Proteases are enzymes that cleave proteins at single, specific peptide bonds. Proteases can be classified into four generic classes: serine, thiol or cysteinyl, acid or aspartyl, and metalloproteases (Cuypers *et al.*, *J. Biol. Chem.* 257:7086 (1982)). Proteases are essential to a variety of biological activities, such as digestion, formation and dissolution of blood clots, reproduction and the immune reaction to foreign cells and organisms. Aberrant proteolysis is associated with a number of disease states in man and other mammals. The human neutrophil proteases, elastase and cathepsin G, have been implicated as contributing to disease states marked by tissue destruction. These disease states include emphysema, rheumatoid arthritis, corneal ulcers and glomerular nephritis. (Barret, in *Enzyme Inhibitors as Drugs*, Sandler, ed., University Park Press, Baltimore, (1980)). Additional proteases such as plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, and kallikreins play key roles in normal biological functions of mammals. In many instances, it is beneficial to disrupt the function of one or more proteolytic enzymes in the course of therapeutically treating a mammal.

Serine proteases include such enzymes as elastase (human leukocyte), cathepsin G, plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, chymotrypsin, trypsin, thrombin, factor Xa and kallikreins.

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Cathepsin G is another human neutrophil serine protease. Compounds with the ability to inhibit the activity of these enzymes are expected to have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. Chymotrypsin and trypsin are digestive enzymes. Inhibitors of these enzymes are useful in treating pancreatitis. Inhibitors of urokinase and plasminogen activator are useful in treating excessive cell growth disease states, such as benign prostatic hypertrophy, prostatic carcinoma and psoriasis.

The serine protease thrombin occupies a central role in hemostasis and thrombosis, and as a multifactorial protein, induces a number of effects on platelets, endothelial cells, smooth muscle cells, leukocytes, the heart, and neurons (Tapparelli *et al.*, *Trends in Pharmacological Sciences* 14:366-376 (1993); Lefkovits and Topol, *Circulation* 90(3):1522-1536 (1994); Harker, *Blood Coagulation and Fibrinolysis* 5 (Suppl 1):S47-S58 (1994)). Activation of the coagulation cascade through either the intrinsic pathway (contact activation) or the extrinsic pathway (activation by exposure of plasma to a non-endothelial surface, damage to vessel walls or tissue factor release) leads to a series of biochemical events that converge on thrombin. Thrombin cleaves fibrinogen ultimately leading to a hemostatic plug (clot formation), potently activates platelets through a unique proteolytic cleavage of the cell surface thrombin receptor (Coughlin, *Seminars in Hematology* 31(4):270-277 (1994)), and autoamplifies its own production through a feedback mechanism. Thus, inhibitors of thrombin function have therapeutic potential in a host of cardiovascular and non-cardiovascular diseases, including: myocardial infarction; unstable angina; stroke; restenosis; deep vein thrombosis; disseminated

intravascular coagulation caused by trauma, sepsis or tumor metastasis; hemodialysis; cardiopulmonary bypass surgery; adult respiratory distress syndrome; endotoxic shock; rheumatoid arthritis; ulcerative colitis; induration; metastasis; hypercoagulability during chemotherapy; Alzheimer's disease; and Down's syndrome.

Factor Xa is another serine protease in the coagulation pathway. Factor Xa associates with factor Va and calcium on a phospholipid membrane thereby forming a prothrombinase complex. This prothrombinase complex then converts prothrombin to thrombin (Claeson, *Blood Coagulation and Fibrinolysis* 5:411-436 (1994); Harker, *Blood Coagulation and Fibrinolysis* 5 (Suppl 1):S47-S58 (1994)). Inhibitors of factor Xa are thought to offer an advantage over agents that directly inhibit thrombin since direct thrombin inhibitors still permit significant new thrombin generation (Lefkovits and Topol, *Circulation* 90(3):1522-1536 (1994); Harker, *Blood Coagulation and Fibrinolysis* 5 (Suppl 1):S47-S58 (1994)).

A need continues to exist for non-peptidic compounds that are potent and selective protease inhibitors, and which possess greater bioavailability and fewer side-effects than currently available protease inhibitors. Accordingly, new classes of potent protease inhibitors, characterized by potent inhibitory capacity and low mammalian toxicity, are potentially valuable therapeutic agents for a variety of conditions, including treatment of a number of mammalian proteolytic disease states.

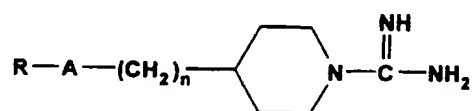
U.S. Patent No. 5,260,307, issued November 9, 1993, discloses amidinopiperidine compounds that inhibit thrombin-induced platelet aggregation and clotting of fibrinogen in plasma. See, for example, column 5, lines 11-63 and column 9, lines 13-16.

European patent application EP 559046, published September 8, 1993, discloses guanidine derivatives having specificity for the inhibition of thrombin. The compounds are useful for inhibiting platelet aggregation induced by thrombin and thrombin-induced clotting of fibrinogen in blood plasma.

-4-

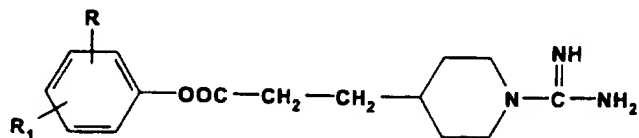
PCT International application WO 94/20467, published September 15, 1994, discloses 4-aminopyridine derivatives that also include an aryl ether or arylamino moiety. The compounds are useful for inhibiting thrombin.

U.S. Patent No. 4,433,152, issued February 21, 1984, discloses
 5 1-piperidinecarboxamides having the formula:



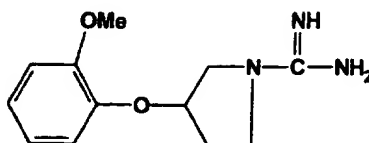
including compounds where n is 0-3, A is oxygen or sulfur, and R is phenyl substituted with alkoxy, sulfamoyl ($-\text{SO}_2\text{NH}-$) or benzyl. See column 2, lines
 10 4-36. The patent discloses that these compounds can be employed to inhibit a complement reaction, inflammation caused by an allergic reaction, and platelet aggregation.

Laid-open application Jpn. Kokai Tokkyo Koho JP 58194861 A2, published November 12, 1983, discloses preparation of piperidine derivatives by
 15 reaction of 1-amidino-4-piperidinepropionic acid or its reactive derivatives with 2,4-RR₁C₆H₃OH, optionally followed by deprotection. Thus, compounds were formed having the formula:



where R can be methoxy and R₁ can be 2-propenyl. Platelet aggregation
 20 inhibitory activity was shown in rabbit platelet-rich plasma.

U.S. Patent No. 3,577,432, patented May 4, 1971, discloses 1-substituted-3-phenoxypyrrolidines and their salts. One compound disclosed therein has the formula:

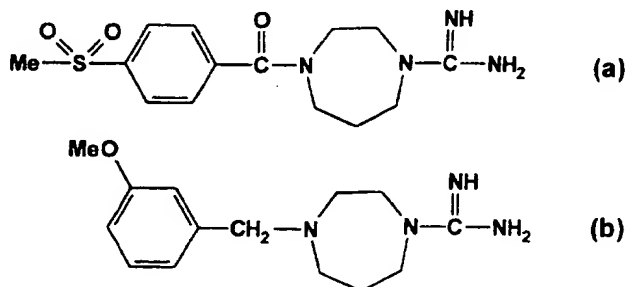


5 The patent discloses that the compounds and their salts can be employed as tranquilizers, muscle relaxants and anticonvulsants.

10 *Chemical Abstracts* 82:140187 (1974) discloses hemisulfate salts of 1-benzyl-4-guanylpiperazines wherein the phenyl ring is optionally substituted with Me, Cl, OMe, SMe and SPh. The compounds are alleged to have hypotensive, antiarrhythmic, local anesthetic, spasmolytic, myorelaxant, and central depressant activity.

15 *Chemical Abstracts* 83:188217 (1975) reports that 2-(2-methoxyphenoxy)ethylguanidine was the most potent compound among a series of 24 guanidine and amidine derivatives in depleting noradrenaline in sympathetic nerve terminals of the guinea pig heart *in vivo*.

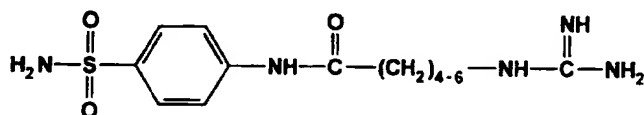
Laid-open application Jpn. Kokai Tokkyo Koho JP 50 140474 A, published November 11, 1975 discloses the following N-amidinodiazepine derivatives including:



Ryznerski *et al.*, "Synthesis and pharmacological properties of phenoxyethylpiperazine derivatives," *Pol. J. Pharmacol. Pharm.* 41:191-199 (1989) discloses 2,6-dimethoxyphenoxyethylpiperazine and the 4-amidine derivative thereof. The compounds were tested for their effect on arterial blood pressure in normotensive rats and their effect upon isolated rat heart.

Jameson *et al.*, "Affinity Chromatography of Bovine Trypsin: A Rapid Separation of Bovine α - and β -Trypsin," *Biochem J.* 141:555-565 (1974) reports on the trypsin-binding ability of affinity columns that comprise a trypsin-substrate coupled to cellulose or Sepharose 40. 4-Amino-N-[[4-[(4-aminoiminomethyl)-amino]butyl]amino]sulfonylphenyl-N-methylbenzenesulfonamide was disclosed as a trypsin-substrate.

Laid-open application Jpn. Kokai Tokkyo Koho JP 51 75042 A2, published June 29, 1976, discloses compounds having the formula:

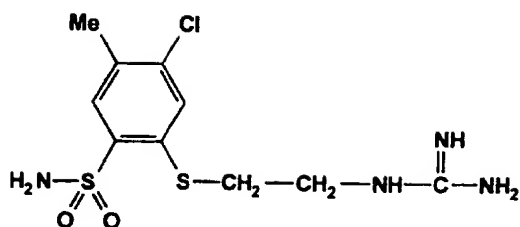


The application discloses that these compounds are effective against *ascites sarcoma* in mice.

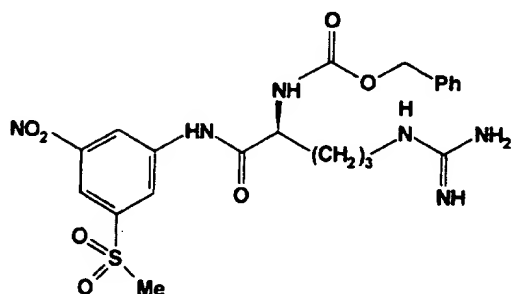
European application EP 372,486, published June 13, 1990, discloses N-amidobenzoyl- β -alanines and analogs thereof that are useful as fibrinogen antagonists.

Chemical Abstracts 110:212261 (1987) discloses a number of 2-mercaptobenzenesulfonamide derivatives, including a compound having the formula:

-7-



Somorin *et al.*, "Synthesis of New Arginine Derivatives as Substrates of Trypsin," *Bull. Chem. Soc. Jpn.* 59:1593-1595 (1986) discloses a compound having the formula:



The reference teaches that this compound is a chromogenic arginine substrate for trypsin hydrolysis.

Chemical Abstracts 63:525c (1965) discloses the compound 4-chloro-5-(2-guanidylethylamino)benzene-1,3-disulfonamide. The abstract further discloses that this compound is an effective diuretic.

Summary of the Invention

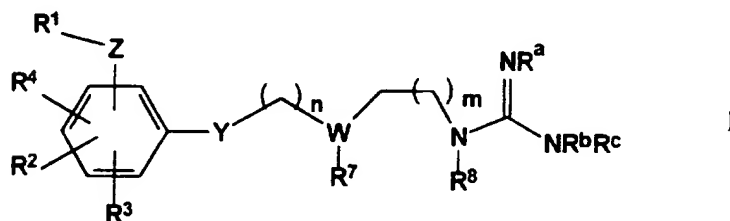
The present invention is directed to novel compounds having Formula I (below). Also provided are processes for preparing compounds of Formula I.

-8-

The novel compounds of the present invention are potent inhibitors of proteases, especially serine proteases, such as chymotrypsin, trypsin, thrombin, plasmin and factor Xa. Certain of the compounds exhibit antithrombotic activity via direct inhibition of thrombin, or are intermediates useful for forming compounds having antithrombotic activity. Other compounds are inhibitors of trypsin and/or chymotrypsin, and are therefore useful in treating pancreatitis. Also provided are methods of inhibiting or treating aberrant proteolysis in a mammal and methods of treating thrombosis, ischemia, stroke, restenosis or inflammation in a mammal by administering an effective amount of a compound of Formula I. Further provided are pharmaceutical compositions comprising a compound of Formula I and one or more pharmaceutically acceptable carriers or diluents.

Detailed Description of the Preferred Embodiments

Compounds of the present invention include compounds of Formula I:



or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

R^1 is one of C_{6-12} alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}C(R^yR^z)-$, $-C(R^yR^z)NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OC(R^yR^z)-$, $-C(R^yR^z)O-$, $-NR^{10}CO-$ or $-CONR^{10}-$, where

R³ and R² are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy; and R¹⁰ is defined below;

5 R², R³ and R⁴ are each independently one of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamido, -CO₂R^x, -CH₂OR^x or -OR^x, or when present on adjacent carbon atoms R² and R³ may also be taken together to form one of -CH=CH-CH=CH- or -(CH₂)_q-, where q is from 2 to 6, and R⁴ is defined as above;

10 R^x, in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of -O-, -NR⁵-, -S-, -CR⁵R⁹- or a covalent bond;

W is N or CR¹⁰;

15 R⁷ and R⁸ are each independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl, or R⁷ and R⁸ are taken together to form -(CH₂)_y-, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

20 R⁵, in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxyalkyl;

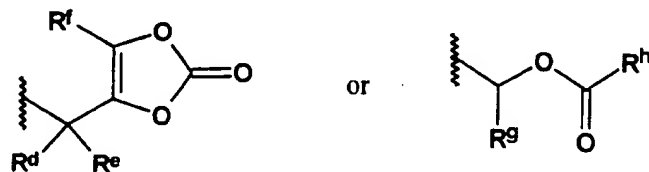
R⁹ is one of alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

25 R¹⁰ is hydrogen, aryl, aralkyl, alkyl, alkyloxyalkyl, wherein said alkyl or alkyloxyalkyl may be substituted by a single amino, monoalkylamino, dialkylamino, carboxy, or by one or more hydroxy groups, wherein the hydroxy groups can be further substituted by alkyl, hydroxyalkyl, alkyloxyalkyl, hydroxyalkyloxyalkyl or alkylcarbonyl groups and wherein two vicinal hydroxy groups can each be linked by an alkylidene group; or R¹⁰ can form the group -E-P(O)R¹¹R¹², where E is alkylene, preferably having one to 4 carbon atoms; and R¹¹ and R¹² are independently C₁₋₆alkyl groups;

-10-

R^a , R^b and R^c are independently hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbonyloxy, cyano or $-\text{CO}_2R^w$, where

R^w is alkyl, cycloalkyl, phenyl, benzyl,



5 where R^d and R^e are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^f is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^g is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, and R^h is aralkyl or C_{1-6} alkyl;

n is from zero to 8, with the proviso that when W is N and Y is other than $-\text{CR}^5\text{R}^9-$, then n is from 2 to 8; and

10 m is from zero to 4, provided that when (a) W is N , or (b) W is C , R^7 and R^8 together form $-(\text{CH}_2)_y-$ and y is 2, then m is not zero.

One preferred group of compounds are compounds of Formula I wherein:

15 R^1 is one of C_{6-12} alkyl, cycloalkyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted by one or more of hydroxy, nitro, trifluoromethyl, halogen, alkoxy, cyano, amino, monoalkylamino, dialkylamino, carboxyalkoxy, mono(carboxyalkyl)amino, di(carboxyalkyl)amino, amidino, guanidino, trifluoromethoxy or perfluoroethoxy, and wherein said aryl, heteroaryl, cycloalkyl and aralkyl may further be optionally substituted by one or more alkyl moieties;

20 Z is one of $-\text{NR}^{10}\text{SO}_2-$, $-\text{SO}_2\text{NR}^{10}-$, $-\text{NR}^{10}\text{CH}_2-$, $-\text{CH}_2\text{NR}^{10}-$, $-\text{OSO}_2-$, $-\text{SO}_2\text{O}-$, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$;

R^2 , R^3 and R^4 are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, $-\text{CO}_2R^x$, $-\text{CH}_2\text{OR}^x$ or $-\text{OR}^x$, or when present on adjacent carbon

atoms, R^2 and R^3 may also be taken together to form one of $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-(\text{CH}_2)_q-$, where q is from 2 to 6, and R^4 is defined as above;

R^x , in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y , W , R^7 , R^8 , R^9 , n and m are defined above; and

R^5 and R^{10} , in each instance, are independently one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or carboxyalkyl.

A second preferred subgenus of compounds falling within the scope of the present invention include compounds of Formula I wherein:

R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6}) alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkyl, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy;

Z is one of $-\text{SO}_2\text{O}-$, $-\text{SO}_2\text{NR}^{10}-$, $-\text{C}(\text{R}^y\text{R}^z)\text{O}-$ or $-\text{OC}(\text{R}^y\text{R}^z)-$, where R^y and R^z are each hydrogen;

R^2 , R^3 and R^4 are independently one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamido, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkoxymethyl or C_{1-4} alkoxy; or alternatively, R^2 and R^3 , when present on adjacent carbon atoms, may also be taken together to form one of $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-(\text{CH}_2)_q-$, where q is from 2 to 6, and R^4 is as defined above;

Y is one of $-\text{O}-$, $-\text{S}-$, $-\text{NR}^{10}-$, or a covalent bond;

-12-

R^6 is one of hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, mono(C_{1-4})alkylamino(C_{2-8})alkyl, di(C_{1-4})alkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

5 R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$ where y is zero, 1 or 2;

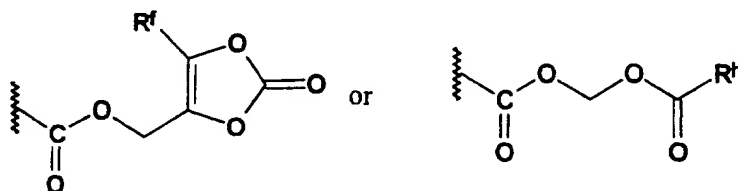
R^5 , in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

10 R^9 is one of C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^{10} is hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{1-6} alkyloxy(C_{1-6})alkyl, wherein said C_{1-6} alkyl or C_{1-6} alkyloxy(C_{1-6})alkyl may be substituted by a single amino, C_{1-4} monoalkylamino, di(C_{1-4})alkylamino, carboxy, or by one or more
15 hydroxy groups, or R^{10} can form the group $-E-P(O)R^{11}R^{12}$, where E is alkylene, preferably having one to 4 carbon atoms; and R^{11} and R^{12} are independently C_{1-6} alkyl groups;

R^a , R^b and R^c are each one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl, benzyloxycarbonyl, cyano,

20



where R^h is benzyl, methyl, ethyl, isopropyl, *sec*-butyl or *t*-butyl, and where R^f is hydrogen or C_{1-6} alkyl;

n is from zero to 8, with the proviso that when W is N, then n is from 2 to 8; and

25

m is from zero to 4, provided that when W is N, then m is not zero.

-13-

An especially preferred subgenus of compounds include compounds of Formula I wherein:

R^1 is one of phenyl or naphthyl, optionally substituted by one or two of chloro, trifluoromethyl, amino or dimethylamino;

5 Z is one of $-\text{SO}_2\text{O}-$, $-\text{SO}_2\text{NR}^{10}-$, $-\text{CH}_2\text{O}-$ or $-\text{OCH}_2-$;

R^2 and R^3 are each hydrogen or R^2 and R^3 may also be taken together to form $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$;

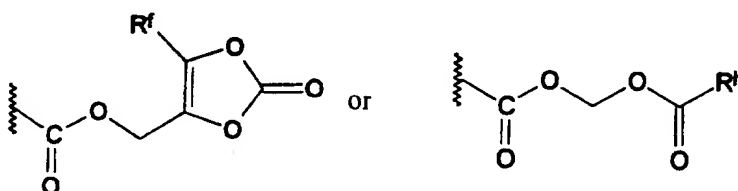
R^4 is one of hydrogen, methyl, methoxy or trifluoromethyl;

Y is one of $-\text{O}-$, $-\text{NR}^{10}-$ or a covalent bond, where R^{10} is defined below;

10 R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl, or R^7 and R^8 are taken together to form $-(\text{CH}_2)_y-$, where y is zero, 1 or 2;

15 R^{10} is independently hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

R^a , R^b and R^c are hydrogen, hydroxy,

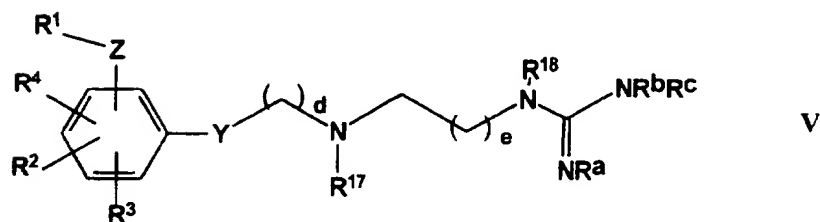
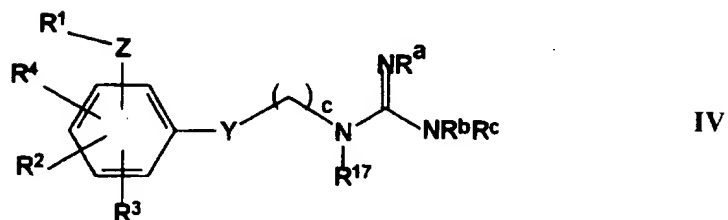
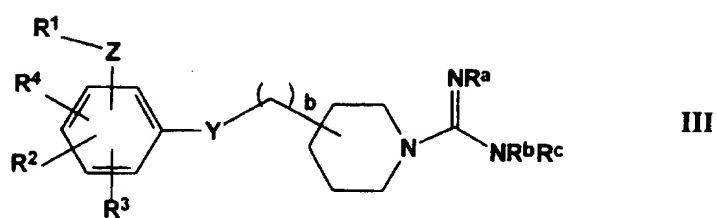
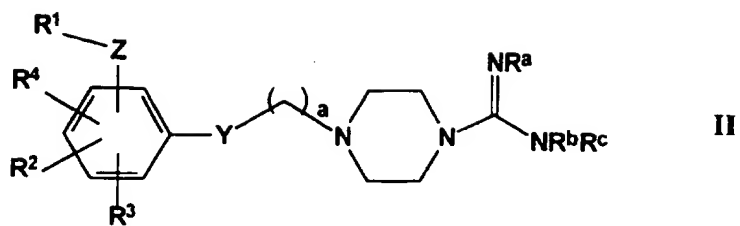


where R^h is benzyl or *t*-butyl, and where R^f is hydrogen or methyl;

n is from zero to 4; and m is zero, 1, 2 or 3.

20 Other preferred groups of compounds falling within the scope of the present invention include compounds of the following formulas:

-14-



5

or solvates, hydrates or pharmaceutically acceptable salts thereof; wherein

 Z , Y , R^1 , R^2 , R^3 , R^4 , R^a , R^b and R^c are defined as above;

R^{17} and R^{18} are each independently one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or carboxyalkyl;

a is from 1 to 8, provided that when Y is other than $-CR^9R^{10}-$, then a is from 2 to 8;

5 b is from 0 to 8;

c is from 1 to 14, provided that when Y is other than $-CR^5R^9-$, then c is from 2 to 14;

d is from 1 to 8, provided that when Y is other than $-CR^5R^9-$, then d is from 2 to 8; and

10 e is from 1 to 4.

The moiety $-Z-R^1$ of Formulae *I-V* is attached to the benzene ring in a position *ortho*-, *meta*- or *para*- to Y, preferably *ortho*- or *meta*-.

Preferred values of Y for compounds of the present invention are divalent oxygen ($-O-$) or $-NR^{10}-$ and preferred values of Z are $-SO_2NR^{10}-$, $-SO_2O-$ or $-CH_2O-$.

Preferred values of R^1 for compounds of the present invention are C_{6-12} alkyl, C_{4-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl or C_{6-14} aryl, especially C_{6-10} aryl, any of which is optionally substituted. Substituents that can be optionally present on the R^1 moieties include one or more, preferably one or two, hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono(C_{1-6})alkylamino, di(C_{1-6})alkylamino, amidino, guanidino, carboxyalkoxy, carboxyalkylamino, cyano, trifluoromethoxy, or perfluoroethoxy. An additional set of preferred values of optional substituents on R^1 include hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6} alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino,

formyliminoamino, C₂₋₆ carboxyalkoxy, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy.

Another set of preferred values for R¹ when R¹ is heteroaryl or substituted heteroaryl includes pyridyl, thienyl, chromenyl, benzoxazolyl, quinazolinyl, quinolinyl and tetrahydroquinolinyl. Preferred substituents when R¹ is substituted heteroaryl include one or more substituents independently selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, amidino, guanidino, carboxyalkoxy, carboxyalkylamino, amino, monoC₁₋₆alkylamino and/or di(C₁₋₆)alkylamino.

Useful values of R¹ include phenyl, chlorophenyl, iodophenyl, dichlorophenyl, bromophenyl, trifluoromethylphenyl, di-(trifluoromethyl)phenyl, methylphenyl, methoxyphenyl, dimethoxyphenyl, hydroxyphenyl, carboxyphenyl, methylaminophenyl, *n*-butylaminophenyl, amidinophenyl, guanidinophenyl, methoxycarbonylphenyl, naphthyl, hydroxynaphthyl, *t*-butylphenyl, cyclohexyl, cyclopentyl, 2-propylbutyl, quinolinyl and tetrahydroquinolinyl. Additional useful values of R¹ include aminophenyl, formyliminoaminophenyl, acetimidoylaminophenyl, methoxycarbonylphenyl, ethoxycarbonylphenyl and carboxymethoxyphenyl.

The groups R², R³ and R⁴ in Formulae I-V substitute for any remaining hydrogen atoms on the benzene ring after allowing for attachment of the moiety -Z-R¹. Preferred values for R², R³ and R⁴ independently include hydrogen, C₁₋₄alkyl, C₄₋₇cycloalkyl, C₆₋₁₄aryl, especially C₆₋₁₀aryl, C₆₋₁₀ar(C₁₋₄)alkyl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, -CO₂R^x, or -CH₂CO₂R^x, where R^x, in each instance, is preferably one of, hydrogen, C₁₋₄alkyl or C₄₋₇cycloalkyl. Alternatively, R² and R³, when attached to adjacent carbon atoms on the benzene ring, are one of -CH=CH-CH=CH- or -(CH₂)_q-, where q is from 2 to 6, thereby forming a fused ring. Preferred values of R² together with R³ include -CH=CH-CH=CH-, -CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-. When R² and R³ together form a fused ring, R⁴ is preferably hydrogen.

Useful values of R^2 , R^3 and R^4 include hydrogen, methyl, ethyl, chloro, bromo, trifluoromethyl, hydroxymethyl, methoxy, ethoxy, carboxamide, nitro, phenyl, cyclopropyl, hydroxy, isopropyl, methoxycarbonyl, ethoxycarbonyl and benzyl. Additional useful values of R^2 , R^3 and R^4 include: R^2 and R^3 together forming $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and R^4 is hydrogen.

Preferred values of R^7 and R^8 in Formula I independently include hydrogen, C_{1-6} alkyl, $\text{C}_{6-10}\text{ar}(\text{C}_{1-6})$ alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl or C_{2-7} carboxyalkyl, or R^7 and R^8 are taken together to form $-(\text{CH}_2)_y-$, where y is most preferably 2. Useful values of R^7 and R^8 include hydrogen, methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-carboxymethyl, 3-carboxyethyl and 4-carboxypropyl.

A preferred value of R^5 includes hydrogen. Other preferred values of R^5 , and the preferred values of R^9 , include C_{1-6} alkyl, $\text{C}_{6-10}\text{ar}(\text{C}_{1-6})$ alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl and C_{2-7} carboxyalkyl. Suitable values of R^5 and R^9 include methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-carboxymethyl, 3-carboxyethyl and 4-carboxypropyl.

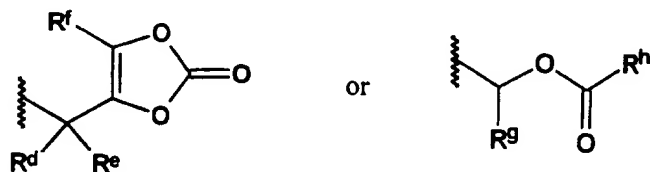
Preferred values of R^{10} include hydrogen, C_{1-6} alkyl, $\text{C}_{6-10}\text{ar}(\text{C}_{1-6})$ alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{2-7} carboxyalkyl, $\text{mono}(\text{C}_{1-4}\text{alkyl})\text{amino}(\text{C}_{1-8})$ alkyl, and $\text{di}(\text{C}_{1-4}\text{alkyl})\text{amino}(\text{C}_{1-8})$ alkyl. Suitable values of R^{10} include methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-aminoethyl, 2-carboxymethyl, 3-carboxyethyl, 4-carboxypropyl and 2-(dimethylamino)ethyl.

Preferred values of R^a , R^b and R^c include hydrogen, C_{1-6} alkyl, cyano or $-\text{CO}_2\text{R}^y$, where R^y , in each instance, is preferably one of, C_{1-4} alkyl or C_{4-7} cycloalkyl. Suitable values of R^b include hydrogen, methyl, ethyl, propyl, *n*-butyl, cyano, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{CH}_2\text{CH}_3$ and $-\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3$. In a more preferred embodiment, R^a , R^b and R^c are each hydrogen. An additional set of preferred values of R^a , R^b and R^c includes hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano or $-\text{CO}_2\text{R}^y$, where R^y is one of C_{1-4} alkyl, C_{4-7} cycloalkyl or

-18-

benzyl. Additional suitable values include hydroxy, methoxy, ethoxy and cyano.

Also preferred at R^a, R^b and R^c is the group -CO₂R^w, where R^w is one of



where R^d-R^h are defined as above. When R^a, R^b and R^c are -CO₂R^w, where R^w is one of one of these moieties, the resulting compounds are prodrugs that possess desirable formulation and bioavailability characteristics. A preferred value for each of R^d, R^e, R^f and R^g is hydrogen, and preferred values for R^h include benzyl and *tert*-butyl.

Preferred values of n include from 1 to 6, more preferably from 1 to 4, and most preferably 1 or 2, with the proviso that when W is N and Y is other than -CR⁹R⁹-, then n is not 1. Preferred values of m include from zero to 4, more preferably zero, 1 or 2, provided that when (a) W is N, or (b) W is C, R⁷ and R⁸ together form -(CH₂)_y- and y is 2, then m is not zero.

Preferred compounds of Formulae *IV* and *V* are those where R¹⁷ and R¹⁸ are independently one of hydrogen, C₁₋₆alkyl, C₆₋₁₀ar(C₁₋₆)alkyl, C₆₋₁₀aryl, C₂₋₁₀hydroxyalkyl and C₂₋₇carboxyalkyl. Most preferred compounds are those where R¹⁷ and R¹⁸ are hydrogen. Useful values of R¹⁷ and R¹⁸ include hydrogen, methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-carboxymethyl, 3-carboxyethyl and 4-carboxypropyl.

Specific compounds within the scope of the invention include the following examples:

2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]phenyl ester,

- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-3-yl]methoxy]phenyl ester,
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester,
- 5 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-3-yl]methoxy]-5-methylphenyl ester,
- 2-chlorobenzenesulfonic acid 3-[2-[1-(aminoiminomethyl)piperazin-4-yl]-ethoxy]phenyl ester diacetic acid salt,
- 10 2-chlorobenzenesulfonic acid 3-[2-[1-(aminoiminomethyl)piperazin-4-yl]ethoxy]-5-methylphenyl ester diacetic acid salt,
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-carbomethoxyphenyl ester,
- 3-(2-chlorobenzoyloxy)-5-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]toluene acetic acid salt,
- 15 N-methyl-N-[2-[(4-aminoiminomethylamino)butyloxy]-4-methylphenyl]-benzenesulfonamide, acetic acid salt,
- N-benzyl-N-[[3-(1-aminoiminomethyl)piperidin-4-ylmethylamino]phenyl]benzenesulfonamide,
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-4-benzylphenyl ester acetic acid salt,
- 20 2-chlorobenzenesulfonic acid 3-[3-(aminoiminomethylamino)propoxy]-5-methylphenyl ester acetic acid salt,
- 2-chlorobenzenesulfonic acid 3-[[4-(aminoiminomethylamino)butoxy]-5-methylphenyl ester acetic acid salt,
- 25 1-naphthalenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
- 3-trifluoromethylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
- benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt.
- 30

- 3-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methoxyphenyl ester,
5 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-4-ethoxycarbonyl-5-methylphenyl ester hydrochloride,
2-trifluoromethylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
3-methylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
10 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-ethylphenyl ester hydrochloride,
2-chlorobenzenesulfonic acid 3-[[5-(aminoiminomethyl)amino]pentoxy]-5-methylphenyl ester hydrochloride,
15 2,3-dichlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride,
2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]naphthalen-1-yl ester hydrochloride,
2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-hydroxymethylphenyl ester,
20 2-[(2-chlorobenzenesulfonyl)[3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid hydrochloride,
2-{benzenesulfonyl-[3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid hydrochloride,
25 2-chloro-N-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl}benzenesulfonamide hydrochloride, and
N-benzyl-N-[[3-(1-(aminoiminomethyl)-piperidin-4-yl)methyl]-carboxymethyl]amino]phenyl]-2-chlorobenzenesulfonamide.

Additional compounds within the scope of the present invention include:

3-methoxybenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

5 3-[(carboxy)methoxy]benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester;

3-hydroxybenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

10 3-(2'-hydroxyethoxy)benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidine-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

3-(2',3'-dihydroxypropoxy)benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

15 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-chlorophenyl ester hydrochloride;

3-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

20 3-aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

2-methoxycarbonylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

4-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride; and

25 4-aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

2-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

30 2-aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

2-chloro-3-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

3-amino-2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester dihydrochloride;

5 2-chlorobenzenesulfonic acid 5-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-2-(ethoxycarbonyl)-3-methylphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 1-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester acetic acid salt;

10 3-(2-chlorobenzyloxy)-1-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]benzene acetic acid salt;

6-((2-chlorobenzenesulfonyl)-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl}amino)hexanoic acid methyl ester hydrochloride;

15 6-((2-chlorobenzenesulfonyl)-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl}amino)hexanoic acid hydrochloride;

6-((2-chlorobenzenesulfonyl)-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-(trifluoromethyl)phenyl}amino)hexanoic acid;

N-(2-propyl)-N-{[3-(1-(aminoiminomethyl)piperidin-4-ylmethoxy]-5-trifluoromethyl}phenyl-2-chlorobenzenesulfonamide hydrochloride;

20 2-chlorobenzenesulfonic acid 3-[[1-(N-methoxycarbonyl-aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester;

2-chlorobenzenesulfonic acid 3-[[1-((N-methoxycarbonylamino)-N-methoxycarbonyliminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester;

25 2-chlorobenzenesulfonic acid 3-[[1-((N,N-di(methoxycarbonyl)-amino)-N-methoxycarbonyliminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester; and

2-chlorobenzenesulfonic acid 3-{N-[[3-(aminoiminomethyl)amino]propyl]-N-(methyl)aminomethyl}phenyl ester acetic acid salt.

30 It is also to be understood that the present invention is considered to include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as

well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds of the present series.

The compounds of Formulae *I-V* may also be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds.

Certain compounds within the scope of Formulae *I-V* are derivatives referred to as prodrugs. The expression "prodrug" denotes a derivative of a known direct acting drug, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic or chemical process; see Notari, R.E., "Theory and Practice of Prodrug Kinetics," *Methods in Enzymology*, 112:309-323 (1985); Bodor, N., "Novel Approaches in Prodrug Design," *Drugs of the Future*, 6(3):165-182 (1981); and Bundgaard, H., "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities," in *Design of Prodrugs* (H. Bundgaard, ed.), Elsevier, New York (1985). Useful prodrugs are those where R^a , R^b and/or R^c are $-CO_2R^*$, where R^* is defined above. See, U.S. Patent No. 5,466,811 and Saulnier *et al.*, *Bioorg. Med. Chem. Lett.* 4:1985-1990 (1994).

The term "alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals of up to 12 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl.

The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, such as phenyl, naphthyl or tetrahydronaphthyl.

The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of

heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranal, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indoliziny, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnoliny, pteridinyl, 4*aH*-carbazolyl, carbazolyl, β -carboliny, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups).

10 The term "aralkyl" or "arylalkyl" as employed herein by itself or as part of another group refers to C₁₋₆alkyl groups as discussed above having an aryl substituent, such as benzyl, phenylethyl or 2-naphthylmethyl.

15 The term "cycloalkyl" as employed herein by itself or as part of another group refers to cycloalkyl groups containing 3 to 9 carbon atoms. Typical examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl.

 The terms "alkoxy" refers to any of the above alkyl groups linked to an oxygen atom.

20 The term "halogen" or "halo" as employed herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine with chlorine being preferred.

 The term "monoalkylamine" as employed herein by itself or as part of another group refers to an amino group which is substituted with one alkyl group having from 1 to 6 carbon atoms.

25 The term "dialkylamine" as employed herein by itself or as part of another group refers to an amino group which is substituted with two alkyl groups, each having from 1 to 6 carbon atoms

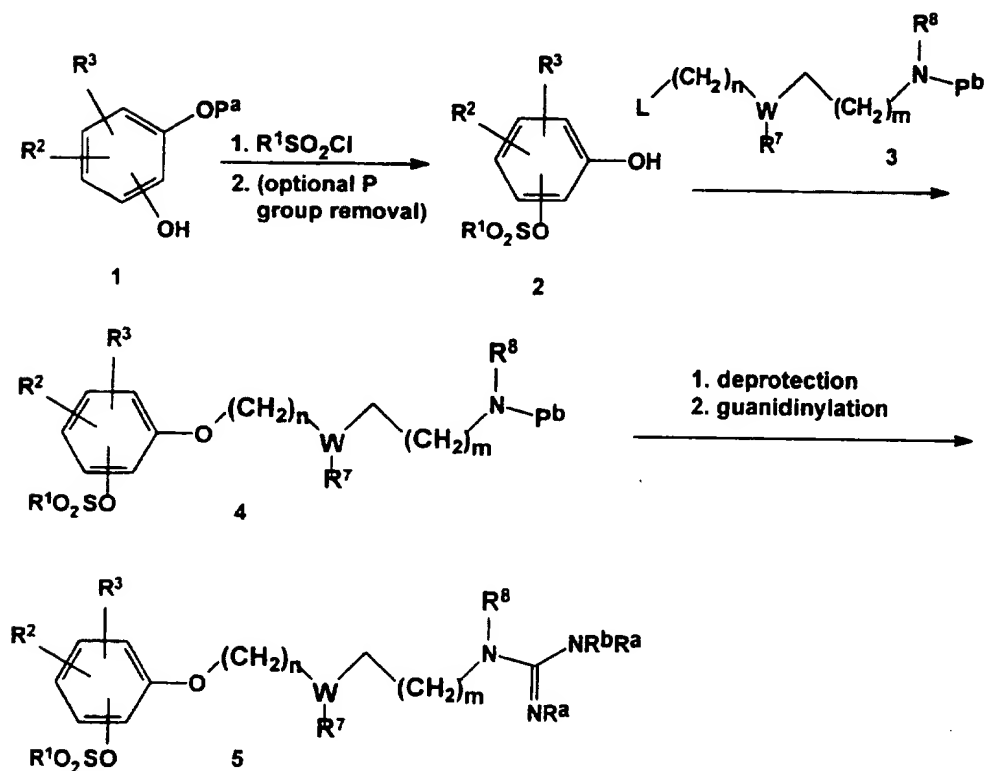
 The term "hydroxyalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more hydroxyl moieties.

The term "carboxyalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more carboxylic acid moieties.

The compounds of the present invention defined by Formulae *I-V* in which Z is $-\text{OSO}_2\text{R}^1$ or Z is $-\text{OCH}_2\text{R}^1$ may be prepared by standard techniques as outlined in Schemes *Ia* and *Ib*.

Scheme *Ia* illustrates the preparation of compounds of the present invention where Z-R¹ is $-\text{OSO}_2-\text{R}^1$.

Scheme Ia



R^1-R^3 , R^7-R^8 , R^a , R^b , R^c , n, and are as defined above; P^a is a hydroxyl protecting group or hydrogen, and P^b is an amino protecting group.

Phenols **1** (where P is H) are converted to monosulfonates **2** by treatment with appropriate sulfonyl chlorides. Preferred conditions include treating phenol **1** with a sulfonyl chloride in a biphasic system composed of ether and an aqueous phase saturated with NaHCO₃. Alternatively, the reaction may be effected first by
5 deprotonating **1** with a strong base, most preferably NaH, in a polar organic solvent, such as DMF or tetrahydrofuran, followed by treating the deprotonated phenol with the sulfonyl chloride. Still alternatively, phenol **1**, in a typical organic solvent, such as methylene chloride, may be converted to **2** by treating the phenol with sulfonyl chloride in the presence of an amine base, such as N-methylmorpholine.

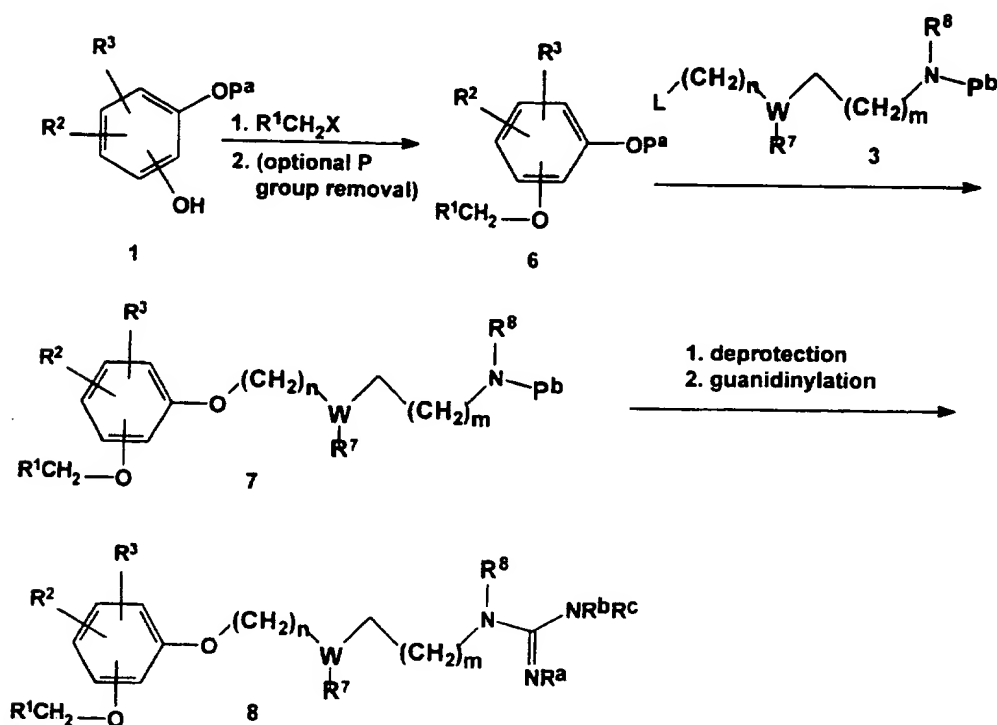
10 Phenols **1** may be monoprotected (P^a is a protecting group) with a variety of protecting groups known in the art, such as esters and benzyl ethers (Green, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). Deprotection of the hydroxyl groups is routinely accomplished using reaction conditions well-known in the art. For example,
15 deprotection of benzyl ethers may be effected through catalytic hydrogenation using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran. Deprotection of an acetate is accomplished by basic hydrolysis, most preferably with sodium hydroxide in aqueous tetrahydrofuran.

Phenols **2** are coupled to **3** (for L = OH) using a Mitsunobu coupling procedure
20 (Mitsunobu, O., *Synthesis* 1 (1981)) to provide **4**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine, in a suitable solvent such as tetrahydrofuran or methylene chloride, and a dialkyl azodicarboxylate, such as diethyl azodicarboxylate. In some cases, it is advantageous to add an amine base such as N-methylmorpholine. The amine terminus of **3** is protected with a
25 protecting group P^b that is readily removed from **4**. Amino-protecting groups are well known in the art (Greene, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). Deprotection of the amino group is effected by employing reaction conditions that are well known in the art. For example, the *t*-butoxycarbonyl (BOC) may be removed by exposure to
30 strongly acidic medium, such as hydrogen chloride, in a suitable solvent, such as

dioxane, or a mixed trifluoroacetic acid/methylene chloride solvent system. Benzyloxycarbonyl (CBz) groups may be removed by hydrogen using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran. The resulting amine is then converted to guanidine **5** using standard reagents such as aminoiminomethanesulfonic acid (Miller, A.E. & Bischoff, J.J., *Synthesis*, 777 (1986)) or 1*H*-pyrazole-1-carboxamide hydrochloride (Bernatowicz, M.S. *et al.*, *J. Org. Chem.* 57(8):2497 (1992)).

Scheme **Ib** illustrates the preparation of compounds of the present invention where Z-R¹ is -O-CH₂-R¹.

10

Scheme Ib

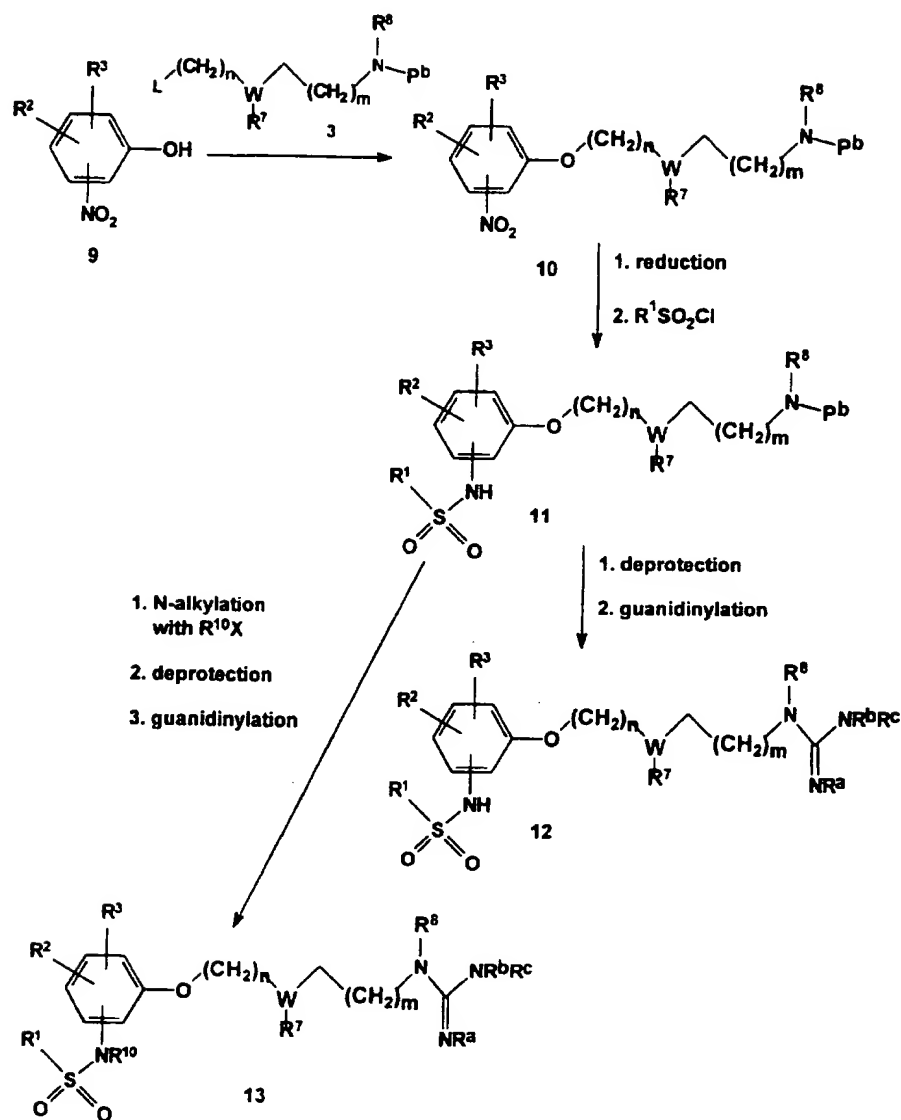
R¹-R³, R⁷-R⁸, R^a, R^b, R^c, n, m, P^a and P^b are as defined above.

Aryl ethers **8** are synthesized in a fashion analogous to synthesis of **5**. Phenol **1** (P is H) is converted to derivative **6** by treating **1** with a strong base.

preferably NaH, in a suitable solvent such as DMF, followed by addition of a reactive alkyl or benzyl compound **4** (where X is a reactive functional group such as iodide, chloride, bromide or alkylsulfonate). Alternatively, the Mitsunobu Reaction may be used with an appropriate R^1CH_2X ($X = OH$) using the reaction conditions described above. The use of suitable alcohol protecting groups (P^a), such as esters, to suppress over-alkylation, is well known in the art (Greene, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). The protecting group may then be removed using well-known techniques, for example by hydrolysis with aqueous NaOH, when an ester protecting group is employed. Phenol **6** is then converted to **8** using the conditions described for formation of **5**.

Scheme II depicts synthetic routes to additional compounds of the present invention.

Scheme II



$\text{R}^1\text{-R}^3$, $\text{R}^7\text{-R}^8$, R^{10} , R^a , R^b , R^c , n, m, P^a and P^b are as defined above.

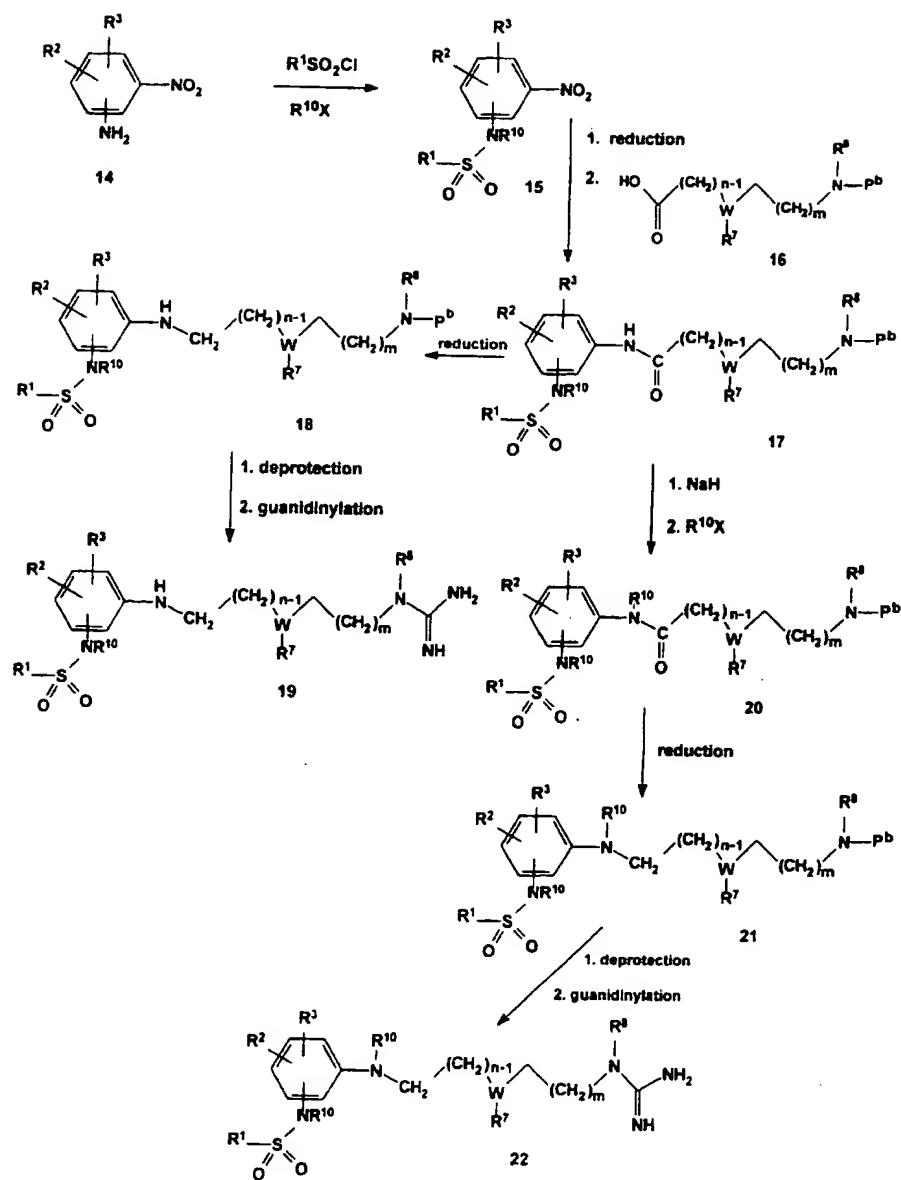
According to Scheme II, a nitrophenol 9 may be coupled to compound 3 by standard techniques. Preferably, the reaction is effected by the Mitsunobu reaction (where L is OH). Alternatively, 9 may be treated with a base, such as NaH, in a suitable solvent such as DMF or THF, followed by addition of 3 (where L is a reactive group, such as Cl, Br, I or alkylsulfonate). The nitro group is

thereafter reduced, for example, by catalytic reduction using palladium on carbon in a suitable solvent such as ethanol or tetrahydrofuran. The resulting product is then treated with an appropriate sulfonyl chloride (R^1SO_2Cl) to provide **11**. Removal of the amine protecting group P^b is accomplished by techniques known
5 in the art. For example, the *t*-butoxycarbonyl (BOC) is removed by exposure to a strongly acidic medium, such as hydrogen chloride in a suitable solvent such as dioxane or trifluoroacetic acid in methylene chloride. Benzyloxycarbonyl (CBz) groups are removed by catalytic hydrogen using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran.

10 The resulting amine is then converted to guanidine **13** using standard reagents such as aminoiminomethanesulfonic acid (Miller, A.E. & Bischoff, J.J., *Synthesis*, 777(1986)) or 1*H*-pyrazole-1-carboxamidine hydrochloride (Bernatowicz, M.S. *et al.*, *J. Org. Chem.* 57(8):2497 (1992)). Alternatively, bis-
15 (*tert*-butoxycarbonyl)/guanylpurazole (Michael S. Bernatowicz, M.S. *et al.*, *Tetrahedron Lett.* 34(2):3389 (1993)) may be used, which, after deprotection with an acidic medium, such as HCl or trifluoroacetic acid, provides **13**. N-Substituted sulfonamide derivative **12** is obtained by alkylation of **11** employing a suitable alkylating agent ($R^{10}X$) in the presence of a base, most preferably Cs_2CO_3 using a polar solvent such as DMF. Deprotection and guanidinylation are then
20 executed in a manner similar to the conversion of **11** to **13**.

Additionally, compounds of the present invention may be prepared by Scheme III.

Scheme III

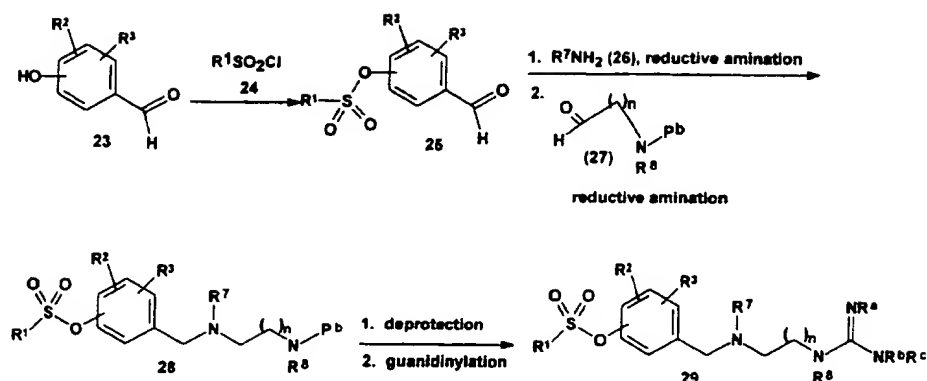


$\text{R}^1\text{-R}^3, \text{R}^7, \text{R}^8, \text{R}^{10}, \text{R}^a, \text{R}^b, \text{R}^c, n, m$ and P^b are each as defined above.

According to Scheme III, nitroaniline 14 is converted to a sulfonamide by treatment with an appropriate sulfonyl chloride R^1SO_2Cl in the presence of a weak base, such as N-methylmorpholine. The resulting sulfonamide nitrogen is alkylated with a suitable alkylating agent ($R^{10}X$) in the presence of a base, preferably an alkali metal carbonate such as Cs_2CO_3 or K_2CO_3 , using a polar solvent, such as DMF, to provide intermediate 15. After reduction of the nitro group, the resulting aniline is coupled to a carboxylic acid, 16, to provide amide 17. Amide coupling may be performed using any of a number of common peptide coupling reagents. Preferably, one of 1,3-dicyclohexylcarbodiimide or Castro's reagent (BOP) are employed (B. Castro *et al.*, *Tetrahedron Lett.*:1219 (1975)). Alternatively, 17 may be formed by coupling the aniline with the corresponding acid chloride of acid 16 in the presence of an acid scavenger, such as N-methylmorpholine. Amide 17 is converted to amine 18 by reduction of the amide functionality with an appropriate hydride reagent, preferably borane-THF complex or chlorotrimethylsilane and lithium borohydride. This reaction occurs in a suitable polar solvent, such as THF. Removal of the amine protecting group P^b and formation of the guanidine as described in Scheme II provides the desired compound 19. Alternatively the amide nitrogen may be alkylated using a strong base, such as sodium hydride, in a suitable polar solvent such as DMF, followed by treatment with an alkylating agent ($R^{10}X$) to afford intermediate 20. Reduction of the amide, as executed in the formation of 18, to give 21 followed by deprotection and guanidinylation as previously described provides the analogous compound 22.

Additionally, compounds of the present invention may be prepared by Scheme IV.

Scheme IV



R^1 - R^3 , R^7 , R^8 , R^a , R^b , R^c , n , m and P^b are each as defined above.

Compounds 25 are obtained by treating phenols 23 with an appropriate sulfonyl chloride 24 under standard conditions. Preferred conditions include treating phenol 23 with 24 in the presence of diisopropylethylamine in methylene chloride. Compound 25 is converted to 28 using a set of sequential reductive aminations, first with amine 26, the product of which is coupled to 27, where P^b and R^8 are defined previously. The preferred reducing agent is tetramethylammonium triacetoxyborohydride. Alternatively, sodium triacetoxyborohydride, or sodium cyanoborohydride may be used. Still alternatively, reductive amination may be carried out first by forming an imine (Schiff's base) between amine and the carbonyl component using a catalytic amount of acid such as *p*-toluenesulfonic acid, followed by reduction with sodium borohydride. Still alternatively, the imine may be reduced using catalytic hydrogenation using a catalyst such as palladium on carbon in standard solvents such as ethanol. Conversions of 28 to 29 are accomplished using the conditions defined in Scheme Ia.

It is to be understood that in each of the above-mentioned schemes, an additional substituent, R⁴, may be present on the phenyl ring of the starting material.

For medicinal use, the pharmaceutically acceptable acid addition salts, those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of the organic cation, are preferred. The acid addition salts are obtained either by reaction of an organic base of Formulae I-V with an organic or inorganic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, cyclamic acid, pivalic acid and the like; useful inorganic acids are hydrohalide acids such as HCl, HBr, HI; sulfuric acid; phosphoric acid and the like. Preferred acids for forming acid addition salts include HCl and acetic acid.

The compounds of the present invention represent a novel class of potent inhibitors of metallo, acid, thiol and serine proteases. Examples of the serine proteases inhibited by compounds within the scope of the invention include leukocyte neutrophil elastase, a proteolytic enzyme implicated in the pathogenesis of emphysema; chymotrypsin and trypsin, digestive enzymes; pancreatic elastase, and cathepsin G, a chymotrypsin-like protease also associated with leukocytes; thrombin and factor Xa, proteolytic enzymes in the blood coagulation pathway. Inhibition of thermolysin, a metalloprotease, and pepsin, an acid protease, are also contemplated uses of compounds of the present invention.

An end use application of the compounds that inhibit chymotrypsin and trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme-inhibiting characteristics of the compounds of the present invention is readily ascertained by standard biochemical techniques well-known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated, as determined

by the attending diagnostician. It is expected that a useful dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of the present invention that are distinguished by their ability to inhibit either factor Xa or thrombin may be employed for a number of therapeutic purposes. As factor Xa or thrombin inhibitors, compounds of the present invention inhibit thrombin production. Therefore, these compounds are useful for the treatment or prophylaxis of states characterized by abnormal venous or arterial thrombosis involving either thrombin production or action. These states include, but are not limited to, deep vein thrombosis; disseminated intravascular coagulopathy which occurs during septic shock, viral infections and cancer; myocardial infarction; stroke; coronary artery bypass; hip replacement; and thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PCTA). The compounds of the present invention may also be used as an anticoagulant in extracorporeal blood circuits.

By virtue of the effects of both factor Xa and thrombin on a host of cell types, such as smooth muscle cells, endothelial cells and neutrophils, the compounds of the present invention find additional use in the treatment or prophylaxis of adult respiratory distress syndrome; inflammatory responses, such as edema; reperfusion damage; atherosclerosis; and restenosis following an injury such as balloon angioplasty, atherectomy, and arterial stent placement.

The compounds of the present invention may be useful in treating neoplasia and metastasis as well as neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.

When employed as thrombin or factor Xa inhibitors, the compounds of the present invention may be administered in an effective amount within the dosage range of about 0.1 to about 500 mg/kg, preferably between 0.1 to 10 mg/kg body weight, on a regimen in single or 2-4 divided daily doses.

When employed as inhibitors of thrombin, the compounds of the present invention may be used in combination with thrombolytic agents such as tissue

plasminogen activator, streptokinase, and urokinase. Additionally, the compounds of the present invention may be used in combination with other antithrombotic or anticoagulant drugs such as, but not limited to, fibrinogen antagonists and thromboxane receptor antagonists.

5 Human leucocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus, compounds of the present invention are expected to have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. Cathepsin G
10 has also been implicated in the disease states of arthritis, gout and emphysema, and in addition, glomerulonephritis and lung infestations caused by infections in the lung. In their end-use application the enzyme inhibitory properties of the compounds of Formulae I-V is readily ascertained by standard biochemical techniques that are well-known in the art.

15 The neutrophil elastase inhibitory properites of compounds within the scope of the present invention are determined by the following method. Neutrophil elastase is prepared by the procedure described by Baugh *et al.*, *Biochemistry* 15: 836 (1979). Enzyme assays are conducted substantially according to the procedure disclosed by Nakajima *et al.*, *J. Biol. Chem.* 254: 4027
20 (1979), in assay mixtures containing 0.10 M Hepes (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) buffer, pH 7.5; 0.5 M NaCl; 10% dimethylsulfoxide; and 1.50×10^{-4} M MeOSuc-Ala-Ala-Pro-Val-*p*-nitroanilide as substrate. Inhibitors are evaluated by comparing enzymatic activity measured in the presence and absence of inhibitor.

25 The Cathepsin G inhibitory properties of compounds within the scope of the present invention are determined by the following method. A preparation of partially purified human Cathepsin G is obtained by the procedure of Baugh *et al.*, *Biochemistry* 15: 836 (1979). Leukocyte granules are a major source for the preparation of leukocyte elastase and cathepsin G (chymotrypsin-like activity).
30 Leukocytes are lysed and granules are isolated. The leukocyte granules are

extracted with 0.20 M sodium acetate, pH 4.0, and extracts are dialyzed against 0.05 M Tris buffer, pH 8.0 containing 0.05 M NaCl overnight at 4°C. A protein fraction precipitates during dialysis and is isolated by centrifugation. This fraction contains most of the chymotrypsin-like activity of leukocyte granules. Specific substrates are prepared for each enzyme, namely MeOSuc-Ala-Ala-Pro-Val-*p*-nitroanilide and Suc-Ala-Ala-Pro-Phe-*p*-nitroanilide. The latter is not hydrolyzed by leukocyte elastase. Enzyme preparations are assayed in 2.00 mL of 0.10 M Hepes buffer, pH 7.5, containing 0.50 M NaCl, 10% dimethylsulfoxide and 0.0020 M Suc-Ala-Ala-Pro-Phe-*p*-nitroanilide as a substrate. Hydrolysis of the *p*-nitroanilide substrate is monitored at 405 nm and at 25°.

Useful dose range for the application of compounds of the present invention as neutrophil elastase inhibitors and as Cathepsin G inhibitors will of course depend upon the nature and severity of the disease state, as determined by the attending diagnostician, with the range of 0.01 to 10 mg/kg of body weight, per day, being useful for the aforementioned disease states.

Compounds of the present invention that inhibit urokinase or plasminogen activator are potentially useful in treating excessive cell growth disease state. As such the compounds of the present invention may also be useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of the present invention are readily ascertained by standard biochemical techniques well-known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Additional uses for compounds of the present invention include analysis of commercial reagent enzymes for active site concentration. For example,

chymotrypsin is supplied as a standard reagent for use in clinical quantitation of chymotrypsin activity in pancreatic juices and feces. Such assays are diagnostic for gastrointestinal and pancreatic disorders. Pancreatic elastase is also supplied commercially as a reagent for quantitation of α_1 -antitrypsin in plasma. Plasma α_1 -antitrypsin increases in concentration during the course of several inflammatory diseases, and α_1 -antitrypsin deficiencies are associated with increased incidence of lung disease. Compounds of the present invention can be used to enhance the accuracy and reproducibility of this assay by titrametric standardization of the commercial elastase supplied as a reagent. See, U.S. Patent No. 4,499,082.

Protease activity in certain protein extracts during purification of particular proteins is a recurring problem which can complicate and compromise the results of protein isolation procedures. Certain proteases present in such extracts can be inhibited during purification steps by compounds of the present invention, which bind tightly to various proteolytic enzymes.

The pharmaceutical compositions of the invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, or ocular routes. Alternatively, or concurrently, administration can be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

In addition to the pharmacologically active compounds, the new pharmaceutical preparations can contain suitable pharmaceutically acceptable

carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

The pharmaceutical preparations of the present invention are manufactured in a manner that is, itself, known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as, starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as, the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as, sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as, magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as, acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as, fatty oils or liquid paraffin. In addition, stabilizers may be added.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, alkaline solutions and cyclodextrin inclusion complexes. Especially preferred alkaline salts are ammonium salts prepared, for example, with Tris, choline hydroxide, Bis-Tris propane, N-methylglucamine, or arginine. One or more modified or unmodified cyclodextrins can be employed to stabilize and increase the water solubility of compounds of the present invention. Useful cyclodextrins for this purpose are disclosed in U.S. Patent Nos. 4,727,064, 4,764,604, and 5,024,998.

In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

Example 1

5 a) **3-Benzoyloxyphenyl acetate:** Resorcinol monoacetate (6.10 g, 40 mmol) in DMF (10 mL) was added dropwise to a mixture of NaH (95%, 0.92 g, 40 mmol) in DMF (50 mL). The reaction mixture was stirred at room temperature for 10 min. Benzyl bromide (6.85 g, 40 mmol) in DMF (10 mL) was added dropwise and stirring was continued at room temperature for 2 h. The reaction was quenched carefully with water (100 mL) and then extracted with ethyl acetate (3x100 mL). The organic phase was washed with brine (2x50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (1:1 hexane:methylene chloride) to give the title compound as a white solid (5.30 g, 55%). ¹H-NMR (300 MHz, CDCl₃) δ 2.28 (s, 3H), 5.03 (s, 2H), 6.72 (m, 2H), 6.85 (dd, 1H), 7.27 (t, 1H), 7.41 (m, 5H).

10 b) **3-Benzoyloxyphenol:** 3-Benzoyloxyphenyl acetate (4.84 g, 20 mmol), as prepared in the preceding step, in tetrahydrofuran (50 mL) was treated with 1 N NaOH (30 mL) for 3 h at room temperature. The mixture was acidified with 1 N HCl and extracted into ethyl acetate (3x100 mL). The organic phase was washed with brine (2x50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (methylene chloride) to give the title compound as a colorless liquid (3.80 g, 96%). ¹H-NMR (300 MHz, CDCl₃) δ 5.01 (s, 2H), 5.09 (s, 1H), 6.47 (m, 2H), 6.56 (dd, 1H), 7.11 (t, 1H), 7.39 (m, 5H).

20 c) **2-Chlorobenzenesulfonic acid 3-benzyloxyphenyl ester:** To a solution of 3-benzyloxyphenol (2.97 g, 15 mmol), as prepared in the preceding step, in methylene chloride (50 mL) at 0°C, was added N,N-diisopropylethylamine (2 mL) and 2-chlorobenzenesulfonyl chloride (3.27 g, 15.5 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 2 h. The reaction mixture was diluted with methylene chloride (200 mL), washed sequentially with saturated NaHCO₃ (2x50 mL) and brine (2x50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash

column chromatography (1:1 hexane:methylene chloride) to give the title compound as a colorless liquid (5.35 g, 95%). ¹H-NMR (300 MHz, CDCl₃) δ 4.97 (s, 2H), 6.71 (dd, 1H), 6.78 (t, 1H), 6.85 (dd, 1H), 7.17 (t, 1H), 7.37 (m, 5H), 7.58 (m, 2H), 7.91 (dd, 1H).

5 **d) 2-Chlorobenzenesulfonic acid 3-hydroxyphenyl ester:** A mixture of 2-chlorobenzenesulfonic acid 3-benzyloxyphenyl ester (3.75 g, 10 mmol), as prepared in the preceding step, and 10% palladium on carbon (350 mg) in tetrahydrofuran (80 mL) was hydrogenated (balloon) for 3 h. The catalyst was filtered through diatomaceous earth and washed with tetrahydrofuran. The combined tetrahydrofuran solutions were evaporated *in vacuo*. The residue was then purified by flash column chromatography (methylene chloride) to give the title compound as a colorless oil (2.75 g, 95%). ¹H-NMR (300 MHz, CDCl₃) δ 6.68 (m, 3H), 7.12 (t, 1H), 7.37 (t, 1H), 7.60 (m, 2H), 7.94 (dd, 1H).

10 **e) N-(tert-butoxycarbonyl)isonipecotic acid:** Isonipecotic acid (3.90 g, 30 mmol), NaHCO₃ (5.05 g, 60 mmol) were dissolved in 1:1 1,4-dioxane:water (100 mL). Di-*tert*-butyl dicarbonate (6.55 g, 30 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo*. The residue was acidified to pH=6 using 10% citric acid and extracted into ethyl acetate (3x100 mL). The organic phase was then washed with brine (2x50 mL), dried over Na₂SO₄, and concentrated *in vacuo* to give the title compound as a white solid (6.25 g, 91%). ¹H-NMR (300 MHz, CDCl₃) δ 1.43 (s, 9H), 1.63 (m, 2H), 1.88 (dd, 2H), 2.45 (m, 1H), 2.83 (t, 2H), 4.00 (d, 2H).

20 **f) N-(tert-Butoxycarbonyl)-4-piperidinemethanol:** N-(*tert*-butoxycarbonyl)-isonipecotic acid (5.73 g, 25 mmol), as prepared in the preceding step, was dissolved in tetrahydrofuran (50 mL) and cooled to 0°C (ice-bath). Borane-tetrahydrofuran complex (1M, 25 mL, 25 mmol) was added slowly over 30 min. The reaction mixture was stirred at 0°C overnight and then warmed up to room temperature for 6 h. Water (10 mL) was added slowly and then K₂CO₃ (5 g in 50 mL water) was added. The reaction mixture was extracted into ethyl acetate (3x50 mL). The organic phase was washed with saturated NaHCO₃.

(2x50 mL), brine (2x50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the title compound as white crystals (4.55 g, 84%). ¹H-NMR (300 MHz, CDCl₃) δ 1.13 (m, 2H), 1.42 (s, 9H), 1.67 (m, 4H), 2.67 (t, 2H), 3.46 (d, 2H), 4.09 (d, 2H).

g) N-(tert-butoxycarbonyl)-4-piperidinemethyl methanesulfonate:

To a solution of N-(tert-butoxycarbonyl)-4-piperidinemethanol (3.23 g, 15 mmol), as prepared in the preceding step, and triethylamine (2 mL) in methylene chloride (100 mL) at 0°C was added slowly methanesulfonyl chloride (1.72 g, 15 mmol). The reaction mixture was stirred at 0°C for 1 hour and then at room temperature for 2 h. The reaction mixture was diluted with methylene chloride (200 mL), washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the title compound as a white solid (4.08 g, 93% yield). ¹H-NMR (300 MHz, CDCl₃) δ 1.24 (m, 2H), 1.46 (s, 9H), 1.75 (d, 2H), 1.92 (m, 1H), 2.71 (t, 2H), 3.02 (s, 3H), 4.07 (d, 2H), 4.13 (m, 2H).

h) 2-Chlorobenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]phenyl ester:

To a solution of 2-chlorobenzenesulfonic acid 3-hydroxyphenyl ester (285 mg, 1.0 mmol), as prepared in step d, in DMF (5 mL) was added NaH (95%, 26 mg, 1.1 mmol). The reaction was stirred under nitrogen for 10 min. N-(tert-Butoxycarbonyl)-4-piperidinemethanol methanesulfonate (293 mg, 1.0 mmol), as prepared in the preceding step, was added and the reaction mixture was stirred at 50°C under nitrogen for 3 h. The reaction mixture was then partitioned between water (50 mL) and ethyl acetate (150 mL). The organic phase was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to give the title compound as a colorless syrup (325 mg, 69%). ¹H-NMR (300 MHz, CDCl₃) δ 1.26 (m, 2H), 1.47

(s, 9H), 1.78 (d, 2H), 1.91 (m, 1H), 2.74 (t, 2H), 3.72 (d, 2H), 4.13 (m, 2H), 6.69 (m, 2H), 6.76 (dd, 1H), 7.16 (m, 1H), 7.37 (t, 1H), 7.62 (m, 2H), 7.95 (dd, 1H).

5 *i) 2-Chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]phenyl ester:* 2-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]-methoxy]phenyl ester (565 mg, 1.2 mmol), as prepared in the preceding step, was treated with 30 mL of 4 N HCl in 1,4-dioxan and stirred at room temperature for 2 h. After removing the solvent *in vacuo*, the residue was purified by flash column chromatography (5% methanol in methylene chloride to 5% methanol in methylene chloride saturated with NH₃)
10 to give the title compound as a white foam (360 mg, 79%). ¹H-NMR (300 MHz, CDCl₃) δ 1.50 (m, 2H), 1.91 (m, 3H), 2.77 (t, 2H), 3.33 (d, 2H), 3.73 (d, 2H), 4.44 (bs, 1H), 6.69 (m, 2H), 6.77 (dd, 1H), 7.16 (t, 1H), 7.37 (t, 1H), 7.62 (m, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₁₈H₂₀NO₄SCl: 382.1 (M+H), 404.1 (M+Na). Found: 382.1, 404.5.

15 *j) 2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]phenyl ester:* A solution of 2-chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]phenyl ester (191 mg, 0.5 mmol), as prepared in the preceding step, in DMF (10 mL) containing triethylamine (0.2 mL) and aminoiminomethanesulfonic acid (124 mg, 1.0 mmol)
20 was stirred at room temperature overnight. The DMF was concentrated *in vacuo* and the residue was purified by flash column chromatography (90:10 methylene chloride:methanol saturated with NH₃) to give the title compound as a white foam (105 mg, 49 %). ¹H-NMR (300 MHz, CDCl₃/DMSO-d₆) δ 1.38 (m, 2H), 1.88 (d, 2H), 2.08 (m, 1H), 3.00 (t, 2H), 3.79 (d, 2H), 4.05 (dd, 2H), 6.61 (dd, 1H), 6.67
25 (t, 1H), 6.79 (dd, 1H), 7.20 (t, 1H), 7.37 (bs, 3H), 7.50 (m, 1H), 7.92 (d, 2H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₁₉H₂₂N₃O₄SCl: 424.1 (M+H), 446.1 (M+Na). Found: 424.3, 446.6

Example 2

a) ***N*-(*tert*-Butoxycarbonyl)-3-piperidinemethanol:** To a solution of 3-piperidinemethanol (4.60 g, 40 mmol) and triethylamine (6 mL) in 1,4-dioxane (100 mL) was added slowly di-*tert*-butyl dicarbonate (8.72 g, 40 mmol). After stirring at room temperature for 2 h, the solvent was then removed *in vacuo* and the residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to give the title compound as a white solid (7.81 g, 91%). ¹H-NMR (300 MHz, CDCl₃) δ 1.25-1.39 (m, 2H), 1.46 (s, 9H), 1.60-1.81 (m, 3H), 1.94 (bs, 1H), 2.98-3.08 (m, 2H), 3.51 (d, 2H), 3.66-3.77 (m, 2H).

b) ***N*-(*tert*-Butoxycarbonyl)-3-piperidinemethanol methanesulfonate:** To a solution of *N*-(*tert*-butoxycarbonyl)-3-piperidinemethanol (3.23 g, 15 mmol), as prepared in the preceding step, and triethylamine (2 mL) in methylene chloride (100 mL) at 0°C was added methanesulfonyl chloride (1.72 g, 15 mmol). After stirring at 0°C for 1 hour, and then at room temperature for 2 h, the reaction mixture was diluted with methylene chloride (200 mL), washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the title compound as a white solid (4.15 g, 94 %). ¹H-NMR (300 MHz, CDCl₃) δ 1.29-1.38 (m, 2H), 1.46 (s, 1H), 1.64-1.98 (m, 3H), 2.80-2.97 (m, 2H), 3.03 (s, 3H), 3.79-3.93 (m, 2H), 4.10 (m, 2H).

c) **2-Chlorobenzenesulfonic acid 3-[[*N*-(*tert*-butoxycarbonyl)piperidin-3-yl]methoxy]phenyl ester:** To a solution of 2-chlorobenzenesulfonic acid 3-hydroxyphenyl ester (570 mg, 2.0 mmol), as prepared in step d of Example 1, in DMF (8 mL) was added NaH (95%, 53 mg, 2.2 mmol). The reaction mixture was stirred under nitrogen for 10 min. *N*-(*tert*-Butoxycarbonyl)-3-piperidinemethanol methanesulfonate (586 mg, 2.0 mmol), as prepared in step b, was added and the reaction mixture was stirred at 40°C under nitrogen overnight. The reaction mixture was diluted with ethyl acetate

(150 mL), washed sequentially with saturated NaHCO_3 (2 x 50 mL) and brine (2 x 50 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to give the title compound as a colorless syrup (510 mg, 54%). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.32 (m, 1H), 1.45 (s, 9H), 1.65-1.98 (m, 4H), 2.88 (m, 2H), 3.73 (m, 2H), 3.79 (d, 2H), 6.69 (m, 2H), 7.13 (t, 1H), 7.37 (t, 1H), 7.61 (m, 2H), 7.94 (d, 1H).

d) 2-Chlorobenzenesulfonic acid 3-[(piperidin-3-yl)methoxy]phenyl ester: 2-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-3-yl]-methoxy]phenyl ester (482 mg, 1.0 mmol), as prepared in the preceding step, was treated with 30 mL of 4 N HCl in 1,4-dioxane and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (5% methanol in methylene chloride to 5% methanol in methylene chloride saturated with NH_3) to give the title compound as a white foam (315 mg, 82%). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.46 (t, 1H), 1.94 (m, 3H), 2.45 (bs, 1H), 2.79 (q, 2H), 3.51 (dd, 2H), 3.75 (t, 1H), 3.83 (t, 1H), 4.63 (bs, 1H), 6.69 (m, 2H), 6.74 (dd, 1H), 7.16 (t, 1H), 7.39 (t, 1H), 7.62 (m, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_4\text{S}$: 382.1 (M+ H). Found: 382.3.

e) 2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-3-yl]methoxy]-phenyl ester: A solution of 2-chlorobenzenesulfonic acid 3-[(piperidin-3-yl)methoxy]phenyl ester (191 mg, 0.5 mmol), as prepared in the preceding step, in DMF (10 mL) containing triethylamine (0.2 mL) and aminoiminomethanesulfonic acid (124 mg, 1.0 mmol) was stirred at room temperature overnight. The DMF was removed *in vacuo* and the residue was purified by flash column chromatography (90:10 methylene chloride:methanol saturated with NH_3) to give the title compound as a white foam (75 mg, 35 %). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 1.42 (m, 2H), 1.70-1.98 (m, 3H), 2.96 (m, 2H), 3.82 (m, 4H), 6.62 (dd, 1H), 6.72 (t, 1H), 6.93 (dd, 1H), 7.29 (t, 1H), 7.39 (bs, 3H), 7.58 (dt, 1H), 7.87 (m, 3H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}_4\text{S}$: 424.1 (M+ H). Found: 424.5.

Example 3

a) **3-Benzoyloxy-5-methylphenol:** Orcinol monohydrate (7.10 g, 50 mmol) in DMF (20 mL) was added dropwise to NaH (95%, 2.4 g, 100 mmol) in DMF (60 mL). The reaction mixture was stirred at room temperature for 20 min. Benzyl bromide (8.55 g, 50 mmol) in DMF (20 mL) was then added dropwise and the reaction mixture was stirred at room temperature for 2 h. Water (100 mL) was added slowly followed by extraction with ethyl acetate (3 x 100 mL). The organic phase was washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was then purified by flash column chromatography (3:1 hexane:ethyl acetate) to give the title compound as a yellow oil (3.15 g, 31 %). ¹H-NMR (300 MHz, CDCl₃) 2.26 (s, 3H), 4.99 (s, 2H), 5.25 (s, 1H), 6.26 (s, 1H), 6.29 (t, 1H), 6.40 (s, 1H), 7.39 (m, 5H).

b) **2-Chlorobenzenesulfonic acid 3-benzoyloxy-5-methylphenyl ester:** A solution of 3-benzoyloxy-5-methylphenol (3.0 g, 15 mmol), as prepared in the preceding step, in methylene chloride (50 mL) at 0 °C was treated with N,N-diisopropylethylamine (2 mL) and 2-chlorobenzenesulfonyl chloride (3.27 g, 15.5 mmol). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 2 h. The reaction mixture was diluted with methylene chloride (200 mL), washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 hexane:methylene chloride) to give the title compound as a colorless liquid (5.10 g, 88%). ¹H-NMR (300 MHz, CDCl₃) δ 2.24 (s, 3H), 4.93 (s, 2H), 6.55 (t, 1H), 6.57 (d, 1H), 6.68 (s, 1H), 7.36 (m, 6H), 7.58 (m, 2H), 7.94 (dd, 1H).

c) **2-Chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester:** A mixture of 2-chlorobenzenesulfonic acid 3-benzoyloxy-5-methylphenyl ester (4.66 g, 12 mmol), as prepared in the preceding step, and 10% palladium on carbon (500 mg) in tetrahydrofuran (80 mL) was hydrogenated (balloon) for 3 h. The catalyst was removed by filtration through diatomaceous earth

(tetrahydrofuran washes) and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (methylene chloride) to give the title compound as a pale-yellow solid (3.20 g, 89%). ¹H-NMR (300 MHz, CDCl₃) δ 2.22 (s, 3H), 5.24 (s, 1H), 6.44 (t, 1H), 6.53 (d, 2H), 7.38 (dt, 1H), 7.60 (m, 2H), 7.96 (dd, 1H).

d) 2-Chlorobenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester: A solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (600 mg, 2.0 mmol), as prepared in the preceding step, N-(tert-butoxycarbonyl)-4-piperidinemethanol, as prepared in step f of Example 1, (430 mg, 2.0 mmol) and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (15 mL) at 0 °C was treated with diethyl azodicarboxylate (349 mg, 2.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 3 h. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic extract was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 ethyl acetate:hexane) to give the title compound as a colorless syrup (895 mg, 90%). ¹H-NMR (300 MHz, CDCl₃) δ 1.24 (m, 2H), 1.47 (s, 9H), 1.80 (d, 2H), 1.89 (m, 1H), 2.24 (s, 3H), 2.72 (t, 2H), 3.68 (d, 2H), 4.13 (m, 2H), 6.47 (t, 1H), 6.52 (d, 1H), 6.58 (d, 1H), 7.38 (t, 1H), 7.61 (m, 2H), 7.97 (dd, 1H).

e) 2-Chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]-5-methylphenyl ester: 2-Chlorobenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)-piperidin-4-yl]methoxy]-5-methylphenyl ester (745 mg, 1.5 mmol), as prepared in the preceding step, was treated with 20 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. After removal of solvent *in vacuo*, the residue was purified by flash column chromatography (10% methanol in methene chloride saturated with NH₃) to give the title compound as a colorless syrup (570 mg, 95%). ¹H-NMR (300 MHz, CDCl₃) δ 1.45 (m, 1H), 1.94 (m, 3H), 2.23 (s, 3H), 2.45 (m, 1H), 2.80 (t, 2H), 3.51 (m, 2H), 3.76 (m, 2H), 6.46 (d, 1H), 6.55 (d,

2H), 7.40 (t, 1H), 7.62 (m, 2H), 7.97 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{19}H_{22}NO_4S$: 396.1 (M+ H). Found: 396.4

f) 2-Chlorobenzenesulfonic acid, 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester: A solution

of 2-chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]-5-methylphenyl ester (396 mg, 1.0 mmol), as prepared in the preceding step, in DMF (10 mL), N,N-diisopropylethylamine (0.5 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol) was stirred at room temperature overnight. The DMF was removed *in vacuo* and the residue was purified by flash column chromatography (90:10 methylene chloride:methanol saturated with NH_3) to give the title compound as a white foam (159 mg, 36 %). 1H -NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 2H), 1.92 (m, 3H), 2.21 (s, 3H), 3.07 (t, 2H), 3.69 (d, 2H), 4.09 (d, 2H), 6.46 (d, 1H), 6.49 (s, 1H), 6.56 (s, 1H), 7.28 (s, 3H), 7.39 (t, 1H), 7.62 (m, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{20}H_{24}N_3O_4S$: 438.1 (M+ H), 460.1 (M+ Na), Found: 438.3, 460.1.

Example 4

a) 2-Chlorobenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-3-yl]methoxy]-5-methylphenyl ester: A solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (600 mg, 2.0 mmol), as prepared in step c of Example 3, N-(tert-butoxycarbonyl)-3-piperidinemethanol (430 mg, 2.0 mmol), as prepared in step a of Example 2, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (15 mL) at 0 °C was treated with diethyl azodicarboxylate (349 mg, 2.0 mmol). The reaction mixture stirred at 0 °C for 2 h and at room temperature for 3 h. Water (50 mL) was added and the reaction mixture was extracted into ethyl acetate (3 x 50 mL). The organic extract was washed sequentially with saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 ethyl acetate:hexane) to give

the title compound as a colorless syrup (875 mg, 88%). ¹H-NMR (300 MHz, CDCl₃) δ 1.28 (m, 1H), 1.45 (s, 9H), 1.64-1.96 (m, 4H), 2.23 (s, 3H), 2.87 (m, 2H), 3.69 (m, 2H), 3.90 (d, 2H), 6.46 (s, 1H), 6.52 (s, 1H), 6.58 (s, 1H), 7.40 (t, 1H), 7.62 (m, 2H), 7.96 (d, 1H).

5 **b) 2-Chlorobenzenesulfonic acid 3-[(piperidin-3-yl)methoxy]-5-methylphenyl ester:** 2-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-3-yl]methoxy]-5-methylphenyl ester (745 mg, 1.5 mmol), as prepared in the preceding step, was treated with 20 mL of 4 N HCl in 1,4-dioxane at room temperature for 2 h. The solvent was removed *in vacuo* and
10 the residue was purified by flash column chromatography (10% methanol in methylene chloride saturated with NH₃) to give the title compound as a colorless syrup (565 mg, 94%). ¹H-NMR (300 MHz, CDCl₃) δ 1.45 (t, 1H), 1.94 (m, 3H), 2.23 (s, 3H), 2.45 (bs, 1H), 2.77 (t, 2H), 3.50 (dd, 2H), 3.76 (m, 2H), 6.46 (d, 1H), 6.55 (d, 2H), 7.40 (dd, 1H), 7.62 (m, 2H), 7.96 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₁₉H₂₂NO₄SCl: 396.1 (M+ H),
15 418.1 (M+Na), Found: 395.8, 418.2.

c) 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-3-yl]methoxy]-5-methylphenyl ester: A solution of 2-chlorobenzenesulfonic acid 3-[(piperidin-3-yl)methoxy]-5-methylphenyl
20 ester (396 mg, 1.0 mmol), as prepared in the preceding step, in DMF (10 mL) containing N,N-diisopropylethylamine (0.5 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol) was stirred at room temperature overnight. The DMF was removed *in vacuo* and the residue was purified by flash column chromatography (90:10 methylene chloride:methanol saturated with NH₃) to give
25 the title compound as a white foam (159 mg, 36 %). ¹H-NMR (300 MHz, CDCl₃) δ 1.45-1.92 (m, 4H), 2.11 (m, 1H), 2.23 (s, 3H), 3.07 (m, 2H), 3.81 (d, 2H), 3.92 (m, 2H), 6.50 (s, 2H), 6.61 (s, 1H), 7.24 (bs, 3H), 7.40 (m, 1H), 7.63 (m, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₄N₃O₄SCl: 438.1 (M+ H), 460.1 (M+Na), Found: 438.5, 460.5.

Example 5

a) *N-(tert-Butoxycarbonyl)-1-(2-hydroxyethyl)piperazine*: To a solution of 1-(2-hydroxyethyl)piperazine (5.20 g, 40 mmol) and triethylamine (6 mL) in 1,4-dioxane (100 mL) was added slowly di-*tert*-butyl dicarbonate (8.72 g, 40 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate to 2% methanol in ethyl acetate) to give the title compound as a colorless oil (8.32 g, 90%). ¹H-NMR (300 MHz, CDCl₃) δ 1.46 (s, 9H), 2.46 (t, 4H), 2.55 (t, 2H), 2.75 (bs, 1H), 3.44 (t, 4H), 3.63 (t, 2H).

b) *2-Chlorobenzenesulfonic acid 3-[2-[N-(tert-butoxycarbonyl)piperazin-4-yl]ethoxy]phenyl ester*: To a solution of 2-chlorobenzenesulfonic acid 3-hydroxyphenyl ester (570 mg, 2.0 mmol), as prepared in step d of Example 1, *N*-(*tert*-butoxycarbonyl)-1-(2-hydroxyethyl)piperazine (507 mg, 2.2 mmol), as prepared in the preceding step, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (15 mL) at 0°C was added diethyl azodicarboxylate (349 mg, 2.0 mmol). After stirring at 0°C for 2 h and at room temperature for 3 h, water (50 mL) was added. The reaction mixture was extracted into ethyl acetate (3 x 50 mL) and washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 ethyl acetate:hexane) to give the title compound as a white solid (875 mg, 85%). ¹H-NMR (300 MHz, CDCl₃) δ 1.47 (s, 9H), 2.49 (t, 4H), 2.77 (t, 2H), 3.45 (t, 4H), 4.02 (t, 2H), 6.72 (m, 2H), 6.78 (dd, 1H), 7.16 (t, 1H), 7.37 (dt, 1H), 7.61 (m, 2H), 7.95 (dd, 1H).

c) *2-Chlorobenzenesulfonic acid 3-[2-(piperazin-1-yl)ethoxy]phenyl ester*: 2-Chlorobenzenesulfonic acid 3-[2-[*N*-(*tert*-butoxycarbonyl)piperazin-4-yl]ethoxy]phenyl ester (994 mg, 2.0 mmol), as prepared in the preceding step, was treated with 4 N HCl (40 mL in 1,4-dioxane) and stirred at room temperature for 2 h. After concentrating *in vacuo*, the residue was purified by flash column

chromatography (10% methanol in methylene chloride saturated with NH_3) to give the title compound as a white foam (705 mg, 88%). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 2.00 (bs, 1H), 2.54 (t, 4H), 2.76 (t, 2H), 2.93 (t, 4H), 4.02 (t, 2H), 6.72 (m, 2H), 6.78 (dd, 1H), 7.16 (t, 1H), 7.37 (dt, 1H), 7.61 (m, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_4\text{SCl}$: 397.1 (M+ H). Found: 397.6.

d) 2-Chlorobenzenesulfonic acid 3-[2-[1-(aminoiminomethyl)piperazin-4-yl]ethoxy]phenyl ester diacetic acid salt: A solution of 2-chlorobenzenesulfonic acid 3-[(piperazin-4-yl)ethoxy]phenyl ester (397 mg, 1.0 mmol), as prepared in the preceding step, N,N-diisopropylethylamine (0.5 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol) in DMF (10 mL) was stirred at room temperature overnight. The DMF was removed *in vacuo* and residue was purified by flash column chromatography (85:15:2 methylene chloride:methanol:acetic acid) to give the title compound as a white solid (290 mg, 52%). $^1\text{H-NMR}$ (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 2.01 (bs, 6H), 2.64 (t, 4H), 2.84 (t, 2H), 3.45 (t, 4H), 4.07 (t, 2H), 6.67 (dd, 1H), 6.77 (t, 1H), 6.83 (dd, 1H), 7.19 (t, 1H), 7.41 (dt, 1H), 7.65 (t, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_4\text{O}_4\text{SCl}$: 439.1 (M+ H), 461.1 (M+Na). Found: 438.8, 460.8.

Example 6

a) 2-Chlorobenzenesulfonic acid 3-[2-[N-(tert-butoxycarbonyl)piperazin-4-yl]ethoxy]-5-methylphenyl ester: A solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (600 mg, 2.0 mmol), as prepared in step c of Example 3, N-(tert-butoxycarbonyl)-1-(2-hydroxyethyl)piperazine (461 mg, 2.0 mmol), as prepared in step a of Example 5, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (15 mL) at 0 °C was treated with diethyl azodicarboxylate (349 mg, 2.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 3 h. Water (50

mL) was added. The reaction mixture was extracted into ethyl acetate (3 x 50 mL), washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 ethyl acetate:hexane) to give the title compound as a white solid (885 mg, 85%). ¹H-NMR (300 MHz, CDCl₃) δ 1.47 (s, 9H), 2.23 (s, 3H), 2.48 (t, 4H), 2.75 (t, 2H), 3.44 (t, 4H), 3.99 (t, 2H), 6.50 (t, 1H), 6.54 (s, 1H), 6.60 (s, 1H), 7.37 (dt, 1H), 7.61 (m, 2H), 7.95 (dd, 1H).

b) 2-Chlorobenzenesulfonic acid 3-[2-(piperazin-4-yl)ethoxy]-5-methylphenyl ester: 2-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)-piperazin-4-yl]ethoxy]-5-methylphenyl ester (1.02 g, 2.0 mmol), as prepared in the preceding step, was treated with 40 mL of 4 N HCl in 1,4-dioxane at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (10% methanol in methylene chloride saturated with NH₃) to give the title compound as a pale-yellow liquid (695 mg, 84%). ¹H-NMR (300 MHz, CDCl₃): δ 1.92 (bs, 2 H), 2.24 (s, 3 H), 2.53 (d, 3 H), 2.73 (t, 2 H), 2.92 (t, 4 H), 3.98 (t, 2 H), 6.50 (t, 1 H), 6.54 (t, 1 H), 6.61 (t, 1 H), 7.38 (dt, 1 H), 7.62 (m, 2 H), 7.97 (dd, 1 H).

c) 2-Chlorobenzenesulfonic acid 3-[2-[1-(aminoiminomethyl)piperazin-4-yl]ethoxy]-5-methylphenyl ester diacetic acid salt: A solution of 2-chlorobenzenesulfonic acid 3-[2-(piperazin-4-yl)ethoxy]-5-methylphenyl ester (411 mg, 1.0 mmol), as prepared in the preceding step, in DMF (10 mL) containing N,N-diisopropylethylamine (0.5 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol) was stirred at room temperature overnight. The DMF was removed *in vacuo* and the residue was purified by flash column chromatography (85:15:2 methylene chloride:methanol:acetic acid) to give the title compound as a white solid (295 mg, 51 %). ¹H-NMR (300 MHz, CDCl₃) δ 1.95 (s, 6H), 2.23 (s, 3H), 2.61 (t, 4H), 2.78 (t, 2H), 3.48 (t, 4H), 3.99 (t, 2H), 6.52 (s, 2H), 6.59 (s, 1H), 7.39 (dt, 1H), 7.62 (m, 2H), 7.96 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid

matrix) calcd. for $C_{20}H_{25}N_4O_4SCl$: 453.1 (M+ H), 475.1 (M+Na). Found: 452.7, 474.9.

Example 7

5 a) **2-Chlorobenzenesulfonic acid 3-hydroxy-5-carbomethoxyphenyl ester:** 2-Chlorobenzenesulfonyl chloride (2.49 g, 0.018 mol) was added dropwise to a rapidly stirred mixture of methyl 3,5-dihydroxybenzoate in saturated sodium bicarbonate (20 mL) and diethyl ether (20 mL) and allowed to stir at ambient temperature. After 2 days, 1.25 g of 2-chlorobenzenesulfonyl chloride was added and stirred for an additional 1 day. The reaction mixture was diluted with
10 methylene chloride and separated. The aqueous layer was extracted with methylene chloride. The combined methylene chloride extracts were washed with brine and water, dried, and evaporated to an oil. The oil was triturated with hexanes (4 times) before placing the residual oil on a silica gel column and eluted first with methylene chloride, then 10% ethyl acetate/methylene chloride. The
15 appropriate fractions were evaporated to give 1.35 g of solid.

 b) **2-Chlorobenzenesulfonic acid 3-[[[1-N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-carbomethoxyphenyl ester:** A solution of triphenylphosphine (0.249 g, 0.95 mol) in tetrahydrofuran (20 mL) was treated with diethyl azodicarboxylate (0.131 mL, 0.83 mol) and allowed to
20 stir at ambient temperature for 15 min. before the addition of 2-chlorobenzenesulfonic acid 3-hydroxy-5-carbomethoxyphenyl ester (0.25 g, 0.73 mol), as prepared in the preceding step, in tetrahydrofuran (5 mL) and N-tert-butoxycarbonyl-4-piperidinemethanol (0.165 g, 0.77 mol), as prepared in step f of Example 1. The reaction mixture was allowed to stir at ambient temperature
25 overnight. The solvent was evaporated and treated with ether/hexane to produce a crystalline material, which was separated by filtration. The filtrate was evaporated to an oil, placed on a silica gel column, and eluted with 20% ethyl acetate/hexane. The appropriate fractions were evaporated to give 0.14 g of

material. ¹H-NMR (CDCl₃; 300 MHz): δ 1.25 (m, 3H), 1.47 (s, 9H), 1.78 (m, 2H), 2.74 (t, 2H), 3.77 (d, 2H), 3.88 (s, 3H), 4.12 (m, 2H), 6.90 (t, 1H), 7.38 (m, 3H), 7.62 (m, 2H), 7.97 (m, 1H).

5 c) 2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-carbomethoxyphenyl ester:

2-Chlorobenzenesulfonic acid 3-[[1-N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-carbomethoxyphenyl ester (0.14 g, 0.26 mmol), as prepared in the preceding step, was treated with 2.5 mL of 25% trifluoroacetic acid in methylene chloride at ambient temperature for 15 min. The solvent was evaporated, the residue was azeotroped with acetonitrile (2 times), and placed under high vacuum. The residue was dissolved in methanol (3 mL) and treated with 1*H*-pyrazole-1-carboxamidine hydrochloride (0.057 g, 0.39 mmol) and *N,N*-diisopropylethylamine (0.136 mL, 0.78 mmol). The reaction mixture was stirred at ambient temperature overnight. An additional portion of 1*H*-pyrazole-1-carboxamidine hydrochloride (10 mg) was added to the reaction mixture and then was stirred for 6 h. The solvent was evaporated to dryness. The residue was triturated with hexane and ether. The residue was dissolved in acetonitrile and diluted with diethylether to produce a crystalline crop, which was collected by filtration to give 25.3 mg of solid. ¹H-NMR (CDCl₃; 300 MHz): δ 1.44-1.55 (m, 2H), 1.95-2.1 (m, 3H), 3.11 (t, 2H), 3.81 (d, 2H), 3.87 (s, 3H), 4.07 (d, 2H), 6.90 (t, 1H), 7.38 (m, 5H), 7.64 (m, 2H), 7.96 (m, 1H). Mass spectrum (MALDI-TOF) calcd. for C₂₁H₂₄N₃O₆SCl: 482.1 (M+ H). Found 483.5.

Example 8

25 a) 3-(2-Chlorobenzoyloxy)-5-methylphenol: To 1.31 g (9.22 mmol) of orcinol monohydrate in 20 mL anhydrous DMF under a nitrogen atmosphere was added 220 mg (9.17 mmol) of NaH (100%). After 5 min, 1.3 mL (100 mmol) of 2-chlorobenzyl bromide was added. The reaction mixture was stirred for 2 h and then quenched with 1 N HCl. The reaction mixture was extracted into

ethyl acetate (200 mL). The organic phase was washed with H₂O (4 x 100 mL), dried (MgSO₄), and concentrated *in vacuo*. Purification by flash chromatography (ether/hexane (50:50 to 100:0)) gave 656 mg of the title compound as a hardened oil. ¹H-NMR (300 MHz, CDCl₃) δ 7.54 (dd, 1 H, J = 3, 7 Hz), 7.39 (dd, 1 H, J = 3, 7 Hz), 7.2 - 7.3 (m, 2 H), 6.41 (s, 1 H), 6.29 - 6.30 (m, 2 H), 5.29 (s, 2 H), and 2.28 (s, 3 H).

b) 3-(2-Chlorobenzyloxy)-5-[1-N-(tert-butoxycarbonyl)piperidin-4-yl]toluene: To 177 mg (0.823 mmol) of N-tert-butoxycarbonyl-4-piperidinemethanol, as prepared in step f of Example 1, 195 mg (0.785 mmol) of 3-(2-chlorobenzyloxy)-5-methylphenol, as prepared in the preceding step, 262 mg (1.02 mmol) of triphenylphosphine, and 250 μL (2.27 mmol) of N-methylmorpholine in 3 mL of tetrahydrofuran was added 140 μL (0.892 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred overnight, quenched with saturated NaCl (50 mL), and extracted into ethyl acetate (50 mL). The organic extract was dried (MgSO₄), and the product was partially purified by flash chromatography (ethyl acetate / hexane (1:4)), to give 230 mg of impure title compound (contaminated with 3-(2-chlorobenzyloxy)-5-methylphenol). This material was used as is in the next reaction.

c) 3-(2-Chlorobenzyloxy)-5-[[piperidin-4-yl]methoxy]toluene: A solution of 230 mg of impure 3-(2-chlorobenzyloxy)-5-[1-N-(tert-butoxycarbonyl)piperidin-4-yl]toluene, prepared in the preceding step, in methylene chloride (1 mL) was added 2 mL of 4 N HCl/dioxane solution. After 3 h, the reaction mixture was quenched with excess 1 N NaOH, extracted into ether (100 mL), dried (MgSO₄), and then purified by flash chromatography (ether/methylene chloride/methanol/NH₄OH (50:43:5:2) then methylene chloride/methanol/NH₄OH (85:10:5)) to give 153 mg of the title compound as an oil. ¹H-NMR (300 MHz, CDCl₃) δ 7.56 (dd, 1 H, J = 3, 7 Hz), 7.39 (dd, 1 H, J = 3, 7 Hz), 7.2 - 7.3 (m, 2 H), 6.42 (s, 1 H), 6.36 (s, 2 H), (5.12 (s, 2 H), 3.76 (d, 2 H), 3.12 (dt, 2 H), 2.64 (dt, 2 H, J = 2.5, 12 Hz), 1.7 - 2.0 (m, 3 H). Mass

-57-

spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{20}H_{24}ClNO_2$: 346.2 (M + H). Found: 346.8.

d) **3-(2-Chlorobenzoyloxy)-5-[[[1-aminoiminomethyl]piperidin-4-yl]methoxy]toluene acetic acid salt:** A solution of 132 mg of 3-(2-chlorobenzoyloxy)-5-[[piperidin-4-yl]methoxy]toluene prepared in the preceding step, 2 mL of DMF, 300 μ L (2.1 mmol) of N,N-diisopropylethylamine, and 124 mg (0.846 mmol) of 1H-pyrazole-1-carboxamide hydrochloride was stirred for 2 days at ambient temperature. The reaction mixture was quenched with 1 N NaOH, extracted into methylene chloride, dried (K_2CO_3), and concentrated *in vacuo*. Purification by chromatography over a 10g Water's Associates 10 g silica Sep-Pak cartridge using elutions of methylene chloride/methanol/acetic acid (89:9.8:1.2 to 78:19.6:2.4) gave 101 mg of the title compound as a colorless solid after removal of solvent. 1H -NMR (300 MHz, CD_3OD) δ 7.73- 7.56 (m, 1 H), 7.40 - 7.45 (m, 1 H), 7.30 - 7.35 (m, 3 H), 6.43 (s, 1 H), 6.37 (s, 1 H), 6.34 (t, 1 H, J = 5.12 (s, 2 H)), 3.93 (d, 2 H), 3.84 (d, 2 H), 3.12 (dt, 2 H, J = 2.5, 13 Hz), 2.0 - 2.25 (m, 2 H), 1.9 (s, 3 H). 1.25 -1.55 (m, 2H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{21}H_{26}N_3ClO_3$: 388.2 (M + H). Found: 387.6.

Example 9

The following compound was synthesized using a process analogous to Example 8:

3-(2-Chlorobenzoyloxy)-1-[[[1-aminoiminomethyl]piperidin-4-yl]methoxy]benzene acetic acid salt: 1H -NMR (300 MHz, DMSO- d_6) δ 7.45 (dd, 1 H), 7.22 - 7.32 (m, 3 H), 6.89 - 7.20 (m, 4 H), 3.88 (d, 2 H), 2.97 (t, 2 H), 1.7 - 2.5 (m, 1 H), 1.23 - 1.31 (m, 2 H). Mass spectrum (MALDI-TOF; α -cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{20}H_{24}ClN_3O_2$: 374.2 (M + H). Found: 374.0.

Example 10

a) 2-[4-(tert-butoxycarbonylamino)butyloxy]-4-methylnitrobenzene: To 252 mg (1.33 mmol) 4-(tert-

butoxycarbonylamino)butanol, 407 mg (2.66 mmol) of 4-methyl-2-nitrophenol
5 and 383 mg (1.46 mmol) of triphenylphosphine in 1.0 mL of anhydrous
tetrahydrofuran under nitrogen was added 336 mL (1.46 mmol) of diethyl
azodicarboxylate. After stirring for 1 h. the mixture was concentrated to a yellow
syrup. Chromatography on a Waters Associates 10 g silica Sep-Pak SPE column
eluting with 10-12 % ethyl acetate-hexane afforded 422 mg (98 %) of the title
10 compound as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ 7.64 (d, 1 H, J=2.0
Hz), 7.30 (dd, 1 H, J=8.5, 2.2 Hz), 6.95 (d, 1 H, J=8.5 Hz), 4.64 (br s, 1 H), 4.09
(t, 2 H, J=6.1 Hz), 3.19 (q, 2 H, J=6.5 Hz), 2.34 (s, 3 H), 1.86 (m, 2 H), 1.69 (m,
2 H), 1.44 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd.
for C₁₆H₂₄N₂O₅: 347.2 (M + H). Found: 347.3.

b) 2-[4-(tert-butoxycarbonylamino)butyloxy]-4-methylaniline: To
15 a solution of 390 mg (1.20 mmol) of 2-[4-(tert-butoxycarbonylamino)butyloxy]-
4-methylnitrobenzene in 1.5 mL of tetrahydrofuran was added 39 mg of 10 %
palladium on carbon and the mixture stirred under a balloon of hydrogen for 20
h. The mixture was filtered (diatomaceous earth) washing with 3 mL of
20 tetrahydrofuran and concentrated to 339 mg (96 %) of the title compound as a
colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ 6.66 (d, 1 H, J=8.0 Hz), 6.55 (dd, 1
H, J=2.0 Hz), 6.49 (d, 1 H, J=8.0 Hz), 4.59 (br s, 1 H), 3.98 (t, 2 H, J=6.3 Hz),
3.19 (q, 2 H, J=6.6 Hz), 2.21 (s, 3 H), 1.82 (m, 2 H), 1.67 (m, 2 H), 1.57 (br s, 2
H), 1.44 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for
25 C₁₆H₂₆N₂O₃: 317.2 (M + Na). Found: 317.2.

**c) N-[2-[4-(tert-butoxycarbonylamino)butyloxy]-4-methylphenyl]
benzenesulfonamide:** To 216 mg (0.734 mmol) of 2-[4-(tert-
butoxycarbonylamino)butyloxy]-4-methylaniline and 101 mL (0.918 mmol) of
4-methylmorpholine in 3.0 mL of dichloromethane was added 143 mL (0.807

mmol) of benzenesulfonyl chloride. The solution was stirred for 45 min, diluted with 30 mL of dichloromethane and washed with 10 % citric acid (2 x 30 mL), saturated NaHCO₃ (2 x 30 mL) and brine (30 mL). The solution was dried (Na₂SO₄) and concentrated to 342 mg of a faintly amber solid. Chromatography on a Waters Associates 10 g silica Sep-Pak SPE column eluting with dichloromethane followed by 4 % ethyl acetate-dichloromethane afforded 282 mg (88 %) of the title compound as a white crystalline solid. ¹H-NMR (300 MHz, CDCl₃) δ 7.72 (m, 2 H), 7.50 (m, 1 H), 7.40 (m, 3 H), 6.94 (s, 1 H), 6.83 (dd, 1 H, J=8.3, 2.1 Hz), 6.59 (d, 1 H, J= 8.3 Hz), 4.54 (br s, 1 H), 3.70 (t, 2 H, J=6.3 Hz), 3.19 (q, 2 H, J=6.5 Hz), 2.27 (s, 3 H), 1.62 (m, 2 H), 1.48 (m, 2 H), 1.46 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₂₂H₃₀N₂O₅S: 457.2 (M + Na). Found: 457.7.

d) *N-methyl-N-[2-[4-(tert-butoxycarbonylamino)butyloxy]-4-methylphenyl]benzenesulfonamide*: To a solution of 176 mg (0.405 mmol) of N - [2 - [4 - (*tert* - b u t o x y c a r b o n y l a m i n o) b u t y l o x y] - 4 - methylphenyl]benzenesulfonamide in 1.5 mL of anhydrous DMF was added 78.4 mg (0.567 mmol) of powdered anhydrous potassium carbonate and 28 mL (0.446 mmol) of iodomethane. After stirring for 18 h, the mixture was partitioned between 20 mL of ethyl acetate and 20 mL of water. The organic layer was washed with water (2 x 15 mL), brine (15 mL), dried (Na₂SO₄) and concentrated to give 180 mg (99 %) of the title compound as a colorless syrup. ¹H-NMR (300 MHz, CDCl₃) δ 7.70 (m, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 7.14 (d, 1 H, J=2.2 Hz), 7.05 (dd, 1 H, J=8.4, 2.2 Hz), 6.68 (d, 1 H, J=8.4), 4.53 (br s, 1 H), 3.61 (t, 2 H, J=6.0 Hz), 3.19 (s, 3 H), 3.06 (q, 2 H, J=6.3 Hz), 2.28 (s, 3 H), 1.46 (s, 9 H), 1.30-1.41 (m, 4 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₂₃H₃₂N₂O₅S: 349.2 (M - BOC + 2H). Found: 349.8.

e) *N-methyl-N-[2-[4-(4-aminoiminomethylamino)butyloxy]-4-methylphenyl]benzenesulfonamide, acetic acid salt*: To a solution of 173 mg (0.386 mmol) of N-methyl-N-[2-[4-(*tert*-butoxycarbonylamino)butyloxy]-4-methylphenyl]benzenesulfonamide in 3.0 mL of anhydrous dichloromethane was

-60-

added 0.75 mL of trifluoroacetic acid. After stirring for 20 min, the solution was concentrated and placed under vacuum (0.1 torr/1 h) to afford 220 mg of a colorless oil. 208 mg of this residue in 2.0 mL of anhydrous DMF was treated with 113 mg (0.772 mmol) of 1*H*-pyrazole-1-carboxamide hydrochloride and 202 mL (1.16 mmol) of *N,N*-diisopropylethylamine and the mixture stirred for 15 h. Water (25 mL) was added and the mixture extracted with ethyl acetate (10 mL). 1 M potassium carbonate (10 mL) was added and the mixture again extracted with ethyl acetate (2 x 15 mL). The combined extracts were washed with 1 M potassium carbonate (15 mL), brine (15 mL), dried (Na₂SO₄) and concentrated to 214 mg of a colorless resin. Chromatography on a Waters Associates 10 g silica Sep-Pak SPE column eluting with a gradient of 1:10:90 to 2:20:80 of acetic acid:methanol:dichloromethane to afford 95 mg of nearly pure title compound as a colorless resin and 148 mg of the title compound contaminated with 1*H*-pyrazole-1-carboxamide. The purer material was crystallized by addition of a solution of the residue in 0.8 mL of acetic acid-methanol (1:1) to 25 mL of ether. After 2.5 days, the solid was collected to afford 51.9 mg (30 %) of the title compound as white crystals. ¹H-NMR (300 MHz, CD₃OD/DMSO-*d*₆, 3:1) δ 7.66 (m, 3 H), 7.55 (m, 2 H), 7.11 (dd, 1 H, *J*=8.4, 2.0 Hz), 6.96 (d, 1 H, *J*=2.0 Hz), 6.86 (d, 1 H, *J*=8.4 Hz), 3.73 (t, 2 H, *J*=6.0 Hz), 3.17 (s, 3 H), 3.15 (t, 2 H, *J*=7.0 Hz), 2.24 (s, 3 H), 1.88 (s, 3 H + xs HOAc), 1.39-1.88 (m, 4 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₁₉H₂₆N₄O₃S: 391.2 (M + H). Found: 391.1.

Example 11

a) *N*-(3-nitrophenyl)benzenesulfonamide: To 6.17 g (44.7 mmol) of 3-nitroaniline and 8.41 mL (48.2 mmol) of *N,N*-diisopropylethylamine in 150 mL of anhydrous ether was added 5.14 mL (40.2 mmol) of benzenesulfonyl chloride. The mixture was heated to reflux under nitrogen with stirring for 16 h, cooled and the resulting two-phase mixture scratched to crystallize the insoluble

oil. After decanting the ether layer, the derived solid was dissolved in 300 mL of dichloromethane and the solution washed with 2 N HCl (3 x 200 mL), saturated NaHCO₃ (200 mL), brine (200 mL), dried (Na₂SO₄) and concentrated to give 9.62 g (86 %) of the title compound as a light tan solid. ¹H-NMR (300 MHz, CDCl₃) δ 7.96 (m, 2 H), 7.86 (m, 2 H), 7.41-7.63 (m, 5 H), 7.30 (br s, 1 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₁₂H₁₀N₂O₄S: 301.0 (M + Na). Found: 301.1.

b) N-benzyl-N-(3-nitrophenyl)benzenesulfonamide: To 6.00 g (21.6 mmol) of N-(3-nitrophenyl)benzenesulfonamide in 15 mL of anhydrous N,N-dimethylformamide at under nitrogen was added 4.48 g (32.4 mmol) of powdered anhydrous potassium carbonate and 2.83 mL (23.8 mmol) of benzyl bromide. After stirring for 3.5 h, the mixture was partitioned between 200 mL of ethyl acetate and 250 mL of water. The aqueous layer was extracted with 50 mL of ethyl acetate and the combined organic phases washed with 1 M K₂CO₃ (2 x 100 mL). 50 mL of hexane was added to the organic phase which was then washed with water (3 x 150 mL), brine (100 mL), dried (Na₂SO₄) and concentrated to give 8.2 g of a crystalline yellow solid. Recrystallization from ethyl acetate-hexane afforded 7.45 g (94 %) of the title compound as cream-colored crystals. ¹H-NMR (300 MHz, CDCl₃) δ 8.06 (d, 1 H, J=7.4 Hz), 7.76 (s, 1 H), 7.64-7.67 (m, 3 H), 7.51-7.56 (m, 2 H), 7.38-7.46 (m, 2 H), 7.21 (s, 5 H), 4.77 (s, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₁₉H₁₆N₂O₄S: 369.1 (M + H), 391.1 (M + Na), 407.0 (M + K). Found: 368.8, 391.3, 407.4.

c) N-benzyl-N-(3-aminophenyl)benzenesulfonamide: To 3.01 g (8.17 mmol) of N-benzyl-N-(3-nitrophenyl)benzenesulfonamide in 60 mL of methanol-tetrahydrofuran (1:1) was added 200 mg of 10 % palladium on carbon. After stirring the mixture under a balloon of hydrogen for 1.7 h, an additional 200 mg of 10 % palladium on carbon was added and stirring was continued for another 2.5 h. Filtration (diatomaceous earth) and concentration afforded a dark green resin which was dissolved in 40 mL of ethyl acetate:hexane (1:1), refiltered (diatomaceous earth) and concentrated to afford 2.9 g of a yellow solid.

Recrystallization from ethyl acetate:ether afforded 2.21 g (80 %) of the title compound as a light orange crystalline powder. ¹H-NMR (300 MHz, CDCl₃) δ 7.68-7.71 (m, 2 H), 7.56-7.62 (m, 1 H), 7.46-7.51 (m, 2 H), 7.18-7.2 (m, 5 H), 6.97 (t, 1 H, J=8.0 Hz), 6.58 (dd, 1 H, J=8.0, 1.6 Hz), 6.47 (t, 1 H, J=2.1 Hz), 6.32 (dd, 1 H, J=8.0, 1.3 Hz), 4.70 (s, 1 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₁₉H₁₈N₂O₂S: 339.1 (M + H), 361.1 (M + Na). Found: 339.5, 361.5.

d) N-benzyl-N-[[3-(1-tert-butoxycarbonylpiperidin-4-yl)carbonylamino]phenyl]benzenesulfonamide: To 149 mg (0.650 mmol) of 1-tert-butoxycarbonylisonipecotic acid, as prepared in step e of Example 1, and 287 mg (0.650 mmol) of Castro's Reagent (benzotriazol-1-yloxytris(dimethylaminophosphonium hexafluorophosphate, BOP) in 1.5 mL of anhydrous DMF was added 155 μL (0.887 mmol) of N,N-diisopropylethylamine and the mixture stirred under nitrogen for 5 min. A solution of 200 mg (0.591 mmol) of N-benzyl-N-(3-aminophenyl)benzenesulfonamide in 0.5 mL of DMF was added. After stirring for 16 h, 10 mL of saturated NaHCO₃ was added. The mixture was partitioned between 25 mL each of ethyl acetate and water. The organic layer was washed with 10 % citric acid (2 x 20 mL), brine (20 mL) and dried (Na₂SO₄). Concentration afforded 360 mg of a yellow resin which was chromatographed on a Waters Associates 10 g silica Sep-Pak SPE column. Elution with a gradient of 5-10 % ethyl acetate:dichloromethane afforded 268 mg (82 %) of the title compound as a white foam. ¹H-NMR (300 MHz, CDCl₃) δ 7.56-7.66 (m, 4 H), 7.47 (m, 2 H), 7.09-7.22 (m, 8 H), 6.60 (br d, 1 H, J=8.0 Hz), 4.70 (s, 2 H), 4.14 (br s, 2 H), 2.74 (br t, 2 H, J=12 Hz), 2.24-2.34 (m, 1 H), 1.84 (br s, 1 H), 1.81 (br s, 1 H), 1.69 (td, 2 H, J=12.2, 4.1 Hz), 1.44 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₃₀H₃₅N₃O₅S: 450.6 (M - BOC + 2 H). Found: 450.3.

e) N-benzyl-N-[[3-(1-tert-butoxycarbonyl)piperidin-4-ylmethylamino]phenyl]benzenesulfonamide: To 293 μL (0.585 mmol) of 2 M lithium borohydride in tetrahydrofuran was added 1.0 mL of tetrahydrofuran

followed by 148 μ L (1.17 mmol) of chlorotrimethylsilane. After stirring for 4 min, 107 mg (0.195 mmol) of N-benzyl-N-[[3-(1-*tert*-butoxycarbonyl)piperidin-4-ylcarbonylamino]phenyl] benzenesulfonamide in 2.0 mL of DMF was added and the mixture heated at 50°C under nitrogen for 20 h. After quenching the reaction with 0.16 mL of MeOH, 1.0 mL of 2 N NaOH was added, the mixture stirred for 10 min and then extracted with ethyl acetate (2 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated to 108 mg of a pale yellow resin. Chromatography on a Waters Associates 5 g silica Sep-Pak SPE column eluting with 5 % ethyl acetate/dichloromethane afforded 93 mg (89%) of the title compound as a colorless resin. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.70-7.74 (m, 2 H), 7.59 (m, 1 H), 7.48 (m, 2 H), 7.22 (m, 5 H), 6.95 (t, 1 H, $J=8.0$ Hz), 6.40 (dd, 1 H, $J=8.1, 2.2$ Hz), 6.25 (t, 1 H, $J=2.1$ Hz), 6.17 (dd, 1 H, $J=7.2, 1.8$ Hz), 4.70 (s, 2 H), 4.11 (br s, 2 H), 3.66 (br s, 1 H), 2.85 (br s, 2 H), 2.66 (t, 2 H, $J=13.3$ Hz), 1.65 (d, 2 H, $J=13.3$ Hz), 1.47 (s, 9 H), 1.09 (m, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_4\text{S}$: 435.6 (M - *tert*-butoxycarbonyl + H). Found: 435.6.

f) N-benzyl-N-[[3-(1-aminoiminomethyl)-piperidin-4-ylmethylamino]phenyl]benzenesulfonamide: To 89.0 mg (0.166 mmol) of N-benzyl-N-[[3-(1-*tert*-butoxycarbonyl)piperidin-4-ylmethylamino]phenyl]benzenesulfonamide in 3.0 mL of anhydrous dichloromethane was added 0.75 mL of trifluoroacetic acid. After stirring for 15 min, the solution was concentrated and placed under vacuum (0.1 torr/1 h) to afford 89 mg of a colorless resin. This residue in 1.5 mL of anhydrous DMF was treated with 48.7 mg (0.332 mmol) of 1*H*-pyrazole-1-carboxamide hydrochloride and 87 mL (0.498 mmol) of N,N-diisopropyl/ethylamine and the mixture stirred for 21 h. An additional 24 mg (0.166 mmol) of 1*H*-pyrazole-1-carboxamide hydrochloride and 58 mL (0.332 mmol) of N,N-diisopropyl/ethylamine and the mixture stirred for 6 h. Finally, an additional 37 mg (0.249 mmol) of 1*H*-pyrazole-1-carboxamide hydrochloride and 87 mL (0.498 mmol) of N,N-diisopropylethylamine and the mixture stirred for 48 h. After concentration to a

5 syrup, 5 mL of 0.1 N NaOH and 30 mL of ethyl acetate were added to the mixture. The solid formed was filtered off, washed with 5 mL of ethyl acetate and placed under vacuum (0.1 torr/1 h) to afford 62.2 mg (78%) of the title compound as a white powder. ¹H-NMR (300 MHz, CD₃OD) δ 7.66-7.72 (m, 3 H), 7.53-7.65 (m, 2 H), 7.16-7.24 (m, 5 H), 6.90 (t, 1 H, J=8.1 Hz), 6.46 (dd, 1 H, J=8.1, 2.0 Hz), 6.22 (t, 1 H, J=2.1 Hz), 6.13 (dd, 1 H, J=7.6, 1.6 Hz), 4.73 (s, 2 H), 3.02 (t, 2 H, J= 13.5 Hz), 2.85 (d, 2 H, J=6.3 Hz), 1.77 (m, 3 H), 1.23 (m, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₂₆H₃₁N₅O₂S: 478.2 (M + H). Found: 478.4.

10

Example 12

a) 2-Chlorobenzenesulfonic acid 3-hydroxy-4-benzylphenyl ester:

At 0°C to a solution of 708 mg (3.54 mmol) of 4-benzylresorcinol in 20 mL of methylene chloride at 0°C was added 410 μL (3.72 mmol) of N-methylmorpholine followed by 740 mg (3.51 mmol) of 2-chlorobenzenesulfonyl chloride. The reaction mixture was warmed to ambient temperature and stirred for 30 min. An additional 400 μL of N-methylmorpholine was added and the reaction mixture was stirred for another 60 min. The reaction mixture was quenched with 1 N HCl, extracted into ether, washed with saturated NaHCO₃, dried (MgSO₄), and purified by flash chromatography (methylene chloride) to give 336.5 mg (25%) of the title compound as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ 7.95 (dd, 1 H, J = 1, 8 Hz), 7.55 - 7.63 (m, 2 H), 7.34 - 7.40 (m, 1 H), 7.1 - 7.3 (m, 5 H), 6.98 (d, 1 H), 6.61 - 6.65 (m, 2 H), 4.95 (s, 1 H), and 3.91 (s, 2 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for C₁₉H₁₅ClO₄S: 375.0 (M + H), 397.0 (M + Na). Found: 373.6, 396.7.

25

b) 2-Chlorobenzenesulfonic acid 3-[[1-N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-4-benzylphenyl ester: To 294 mg (0.787 mmol) of 2-chlorobenzenesulfonic acid 3-hydroxy-4-benzylphenyl ester, as prepared in the preceding step, in tetrahydrofuran (5 mL) containing 236 μL

(1.10 mmol) of N-*tert*-butoxycarbonyl-4-piperidinemethanol, as prepared in step f of Example 1, 300 μ L (2.72 mmol) of N-methylmorpholine, and 309 mg (1.18 mmol) of triphenylphosphine was added 185 μ L (1.18 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at ambient temperature for 1 h, quenched with saturated NaHCO₃, and extracted into ether. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate/hexane (1:2)) gave 382 mg of the title compound as a colorless foam. ¹H-NMR (300 MHz, CDCl₃) δ 7.95 (dd, 1 H, J = 1.5, 8 Hz), 7.55 - 7.64 (m, 2 H), 7.35 - 7.40 (m, 1 H), 7.08 - 7.26 (m, 5 H), 6.93 (d, 2 H, J = 8 Hz), 6.65 (d, 2 H, J = 2, 8 Hz), 6.53 (dd, 1 H, J = 2, 8 Hz), 3.87 (s, 2 H), 3.67 (d, 2 H, J = 6 Hz), 2.69 (t, 2 H, J = 13 Hz), and 1.47 (s, 9 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for C₃₀H₃₄ClNO₆S: 594.2 (M + Na). Found: 594.0, 472.0 (M - (*tert*-butoxycarbonyl) + H).

c) **2-Chlorobenzenesulfonic acid 3-[[piperidin-4-yl]methoxy]-4-benzylphenyl ester:** A solution of 380 mg (0.666 mmol) of 2-chlorobenzenesulfonic acid 3-[[1-N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-4-benzylphenyl ester, as prepared in the preceding step, in 5 mL of methylene chloride was added 3 mL of 4 N HCl in dioxane. The reaction mixture was stirred at ambient temperature for 1 h, carefully quenched with saturated NaHCO₃, dried (K₂CO₃), and concentrated to give 381 mg of crude title compound as an oil which was used as is in the next step. ¹H-NMR (300 MHz, CDCl₃) δ 7.96 (d, 1 H), 7.54 - 7.63 (m, 2 H), 7.34 - 7.40 (m, 1 H), 7.08 - 7.24 (m, 4 H), 6.91 (d, 1 H, J = 8 Hz), 6.66 (d, 1 H, J = 2 Hz), 6.54 (dd, 1 H, J = 2, 8 Hz), 3.88 (s, 2 H), 3.66 (d, 2 H, J = 5 Hz), 3.10 (d, 2 H, J = 12 Hz), 2.62 (t, 2 H, J = 10 Hz), 1.1 - 1.2 (m, 4 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for C₂₅H₂₆ClNO₄S: 472.1 (M + H). Found: 472.6.

d) **2-Chlorobenzenesulfonic acid 3-[[1-aminoiminomethyl]piperidin-4-yl]methoxy]-4-benzylphenyl ester acetic acid salt:** A mixture of 271 mg (0.576 mmol) of 2-chlorobenzenesulfonic acid 3-[[piperidin-4-yl]methoxy]-4-benzylphenyl ester, as prepared in the preceding

step, in 2 mL of DMF, 500 μ L (4.54 mmol) of N,N-diisopropylethylamine, and 196 mg (1.34 mmol) of 1*H*-pyrazole-1-carboxamidine hydrochloride was stirred at ambient temperature for 2 days. The reaction mixture was quenched with 1 N NaOH, extracted into methylene chloride, dried (K_2CO_3), and concentrated. The product was purified by flash chromatography (methylene chloride/methanol/acetic acid (93:6.5:0.5 to 78:19.6:3.4)) to give an oil. Crystallization from a mixture of methylene chloride, methanol and ether gave 146 mg of the title compound. 1H -NMR (300 MHz, CD_3OD) δ 7.92 (dd, 1 H), 7.67-7.78 (m, 2 H), 7.44-7.50 (m, 1 H), 7.03-7.50 (m, 6 H), 6.69 (d, 1 H, $J = 1$ Hz), 6.57 (dd, 1 H, $J = 3, 8$ Hz), 3.71 (d, 2 H, $J = 4.5$ Hz), 3.03 (t, 2 H), 1.94-2.00 (m, 2 H), 1.89 (s, 3 H), 1.70 (d, 2 H), 2.12-1.34 (m, 2 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{26}H_{28}ClN_3O_4S$: 514.2 (M + H), 536.1 (M + Na). Found: 514.4, 536.0.

Example 13

15 a) 2-Chlorobenzenesulfonic acid 3-[[3-*N*-(*tert*-
 butoxycarbonyl)amino]propoxy]-5-methylphenyl ester: A solution of 2-
chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (450 mg, 1.5 mmol),
as prepared in step c of Example 3, *N*-(*tert*-*butoxycarbonyl*)-3-aminopropanol
20 (263 mg, 1.5 mmol) and triphenylphosphine (400 mg, 1.5 mmol) in
tetrahydrofuran (10 mL) at 0°C was treated with diethyl azodicarboxylate (263
mg, 1.5 mmol). The reaction mixture was stirred at 0°C for 2 h and at room
temperature for 3 h. Water (50 mL) was added and the reaction mixture was
extracted with ethyl acetate (3 x 50 mL). The organic extract was washed
sequentially with saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), dried
25 over Na_2SO_4 , and concentrated in *vacuo*. The residue was purified by flash
column chromatography (1:2 ethyl acetate:hexane) to give the title compound as
a colorless liquid (595 mg, 87%). 1H -NMR (300 MHz, $CDCl_3/CD_3OD$) δ 1.44

-67-

(s, 9H), 1.91 (t, 2H), 2.24 (s, 3H), 3.24 (q, 2H), 3.90 (t, 2H), 6.47 (d, 1H), 6.52 (s, 1H), 6.61 (d, 1H), 7.41 (m, 1H), 7.65 (m, 2H), 7.95 (dd, 1H).

b) 2-Chlorobenzenesulfonic acid 3-[[3-(N-tert-butoxycarbonyl) amino]propoxy]-5-methylphenyl ester acetic acid salt:

5 2-Chlorobenzenesulfonic acid 3-[[3-(N-tert-butoxycarbonyl) amino]propoxy]-5-methylphenyl ester (456 mg, 1.0 mmol), as prepared in the preceding step, was treated with 10 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was concentrated from methylene chloride several times to give the amine salt. This was dissolved in
10 DMF (10 mL) and treated with N,N-diisopropylethylamine (1.0 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (3x50 mL), dried over K₂CO₃, and concentrated *in vacuo*. The residue was
15 purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) to give the title compound as a colorless foam (370 mg, 80 %). ¹H-NMR (300 MHz, DMSO-d₆): δ 1.86 (t, 2H), 1.91 (s, 3H), 2.21 (s, 3H), 3.23 (q, 2H), 3.93 (t, 2H), 6.45 (d, 1H), 6.50 (s, 1H), 6.76 (s, 1H), 7.30 (bs, 4H), 7.59 (t, 1H), 7.87 (m, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₁₇H₂₀N₃O₄SCl: 398.1 (M+ H), 420.1 (M+Na),
20 436.0 (M+K). Found: 397.9, 419.8, 435.8.

Example 14

a) 2-Chlorobenzenesulfonic acid 3-[[4-(N-tert-butoxycarbonyl)amino]butoxy]-5-methylphenyl ester: A solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (450 mg, 1.5 mmol),
25 as prepared in step c of Example 3, N-(tert-butoxycarbonyl)-4-aminobutanol (284 mg, 1.5 mmol), and triphenylphosphine (400 mg, 1.5 mmol) in tetrahydrofuran (10 mL) at 0°C was treated with diethyl azodicarboxylate (263 mg, 1.5 mmol).

The reaction was stirred at 0°C for 2 h and at room temperature for 3 h. Water (50 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 50 mL). The organic phase was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 ethyl acetate:hexane) to give the title compound as a colorless liquid (615 mg, 87%).
¹H-NMR (300 MHz, CDCl₃): δ 1.45 (s, 9H), 1.62 (m, 2H), 1.73 (m, 2H), 2.24 (s, 3H), 3.13 (t, 2H), 3.86 (t, 2H), 6.45 (s, 1H), 6.51 (d, 1H), 6.60 (s, 1H), 7.41 (t, 1H), 7.65 (m, 2H), 7.95 (dd, 1H).

b) 2-Chlorobenzenesulfonic acid 3-[[4-(aminoiminomethyl)amino]butoxy]-5-methylphenyl ester acetic acid salt: 2-Chlorobenzenesulfonic acid 3-[[4-(N-*tert*-butoxycarbonyl)amino]butoxy]-5-methylphenyl ester (470 mg, 1.0 mmol), as prepared in the preceding step, was treated with 10 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. The solvent was concentrated *in vacuo* and concentrated from methylene chloride several times to give the amine salt. This was dissolved in DMF (10 mL) and treated with N,N-diisopropylethylamine (1.0 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol). The reaction mixture was stirred at room temperature overnight. The DMF was evaporated *in vacuo*. The residue was dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (2x50 mL), dried over K₂CO₃, and concentrated *in vacuo*. The residue was purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) to give the title compound as a colorless foam (368 mg, 78%).
¹H-NMR (300 MHz, CDCl₃/CD₃OD) δ 1.78 (m, 4H), 1.99 (bs, 3H), 2.24 (s, 3H), 3.18 (t, 2H), 3.90 (t, 2H), 6.49 (d, 2H), 6.61 (s, 1H), 7.44 (t, 1H), 7.67 (m, 2H), 7.95 (dd, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₁₈H₂₂N₃O₄SCl: 412.1 (M+H), 434.1 (M+Na). Found: 412.4, 434.4.

Example 15

a) 1-Naphthalenesulfonic acid 3-benzyloxy-5-methylphenyl ester:

A solution of 3-benzyloxy-5-methylphenol (600 mg, 3.0 mmol), as prepared in step a of Example 3, in methylene chloride (15 mL) at 0°C was treated with N,N-diisopropylethylamine (0.5 mL) and 1-naphthalenesulfonyl chloride (670 mg, 3.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 2 h. The reaction mixture was diluted with methylene chloride (200 mL) and water (50 mL). The organic extract was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 hexane:methylene chloride) to give the title compound as a colorless liquid (1.05 g, 87%). ¹H-NMR (300 MHz, CDCl₃) δ 2.16 (s, 3H), 4.73 (s, 2H), 6.23 (t, 1H), 6.37 (dd, 1H), 6.61 (dd, 1H), 7.28 (m, 5H), 7.48 (t, 1H), 7.67 (t, 1H), 7.77 (t, 1H), 7.97 (t, 1H), 8.12 (dt, 2H), 8.19 (dd, 1H).

b) 1-Naphthalenesulfonic acid 3-hydroxy-5-methylphenyl ester:

A mixture of 1-naphthalenesulfonic acid 3-benzyloxy-5-methylphenyl ester (1.0 g, 2.47 mmol), as prepared in the preceding step, and 10% palladium on carbon (200 mg) in ethanol (20 mL) was hydrogenated (balloon) overnight. The catalyst was removed by filtration through diatomaceous earth (methanol washes) and the filtrate was evaporated *in vacuo* to give the title compound as a colorless syrup (705 mg, 91%). ¹H-NMR (300 MHz, CDCl₃) δ 2.11 (s, 3H), 4.20 (bs, 1H), 6.16 (t, 1H), 6.47 (t, 1H), 7.51 (t, 1H), 7.69 (t, 1H), 7.79 (t, 1H), 7.81 (d, 1H), 8.11 (dt, 2H), 8.77 (dd, 1H).

c) 1-Naphthalenesulfonic acid 3-hydroxy-5-methylphenyl ester:

A solution of 1-naphthalenesulfonic acid 3-hydroxy-5-methylphenyl ester (315 mg, 1.0 mmol), as prepared in the preceding step, N-(*tert*-butoxycarbonyl)-4-piperidinemethanol (215 mg, 1.0 mmol), as prepared in step f of Example 1, and triphenylphosphine (263 mg, 1.0 mmol) in tetrahydrofuran (10 mL) at 0°C was treated with diethyl azodicarboxylate (175 mg, 1.0 mmol). The reaction mixture

-70-

was stirred at 0°C for 2 h and at room temperature for 3 h. Water (50 mL) was added. The reaction mixture was extracted into ethyl acetate (3 x 50 mL), washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:3 ethyl acetate:hexane) to give the title compound as a colorless liquid (285 mg, 56%). ¹H-NMR (300 MHz, CDCl₃) δ 1.16 (m, 2H), 1.47 (s, 9H), 1.70 (m, 2H), 1.78 (m, 1H), 2.15 (s, 3H), 2.70 (t, 2H), 3.48 (d, 2H), 4.11 (m, 2H), 6.16 (d, 1H), 6.32 (s, 1H), 6.51 (s, 1H), 7.49 (t, 1H), 7.68 (t, 1H), 7.79 (t, 1H), 7.80 (d, 1H), 8.14 (d, 2H), 8.81 (d, 1H).

d) 1-Naphthalenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt: 1-Naphthalenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (256 mg, 0.5 mmol), as prepared in the preceding step, was treated with 10 mL of 4 N HCl in 1,4-dioxane at room temperature for 2 h. The solvent was removed *in vacuo* and the residue concentrated from methylene chloride several times to give the amine salt. This was then dissolved in DMF (10 mL) and treated with N,N-diisopropylethylamine (0.5 mL) and aminoiminomethanesulfonic acid (124 mg, 1.0 mmol). The reaction mixture was stirred at room temperature overnight. The DMF was removed *in vacuo*. The residue was partitioned between methylene chloride (200 mL) and 10% K₂CO₃ (50 mL). The organic phase was washed with 10% K₂CO₃ (2x50 mL), dried over K₂CO₃, and concentrated *in vacuo*. The residue was purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) to give the title compound as a colorless foam (142 mg, 58%). ¹H-NMR (300 MHz, CDCl₃) δ 1.25 (m, 2H), 1.84 (m, 3H), 2.05 (bs, 3H), 2.12 (s, 3H), 3.03 (t, 2H), 3.52 (d, 2H), 4.03 (d, 2H), 6.19 (s, 1H), 6.27 (s, 1H), 6.49 (s, 1H), 7.43 (bs, 4H), 7.49 (t, 1H), 7.67 (t, 1H), 7.78 (t, 1H), 7.80 (d, 1H), 8.14 (t, 2H), 8.78 (d, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₄H₂₇N₃O₄S: 454.2 (M+H), 476.2 (M+Na). Found: 454.9, 476.9.

Example 16

a) **3-Trifluoromethylbenzenesulfonic acid 3-benzyloxy-5-methylphenyl ester:** A solution of 3-benzyloxy-5-methylphenol (400 mg, 2.0 mmol), as prepared in step a of Example 3, in methylene chloride (10 mL) at 0°C was treated with N,N-diisopropylethylamine (0.4 mL) and 3-trifluoromethylbenzenesulfonyl chloride (489 mg, 2.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 2 h. The reaction mixture was diluted with methylene chloride (200 mL) and water (50 mL). The organic extract was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 hexane:methylene chloride) to give the title compound as a colorless liquid (710 mg, 85%). ¹H-NMR (300 MHz, CDCl₃) δ 2.25 (s, 3H), 4.94 (s, 2H), 6.41 (s, 2H), 6.72 (s, 1H), 7.37 (m, 5H), 7.68 (t, 1H), 7.91 (d, 1H), 8.03 (d, 1H), 8.09 (s, 1H).

b) **3-Trifluoromethylbenzenesulfonic acid 3-hydroxy-5-methylphenyl ester:** A mixture of 3-trifluoromethylbenzenesulfonic acid 3-benzyloxy-5-methylphenyl ester (633 mg, 1.5 mmol), as prepared in the preceding step, and 10% palladium on carbon (100 mg) in ethanol (20 mL) was hydrogenated (balloon) for 3 h. The catalyst was removed by filtration through diatomaceous earth (methanol washes) and the filtrate was evaporated *in vacuo* to give the title compound as a colorless syrup (485 mg, 97%). ¹H-NMR (300 MHz, CDCl₃/CD₃OD) δ 2.20 (s, 3H), 6.26 (s, 1H), 6.30 (t, 1H), 6.57 (s, 1H), 7.74 (t, 1H), 7.96 (d, 1H), 8.05 (d, 1H), 8.09 (s, 1H).

c) **3-Trifluoromethylbenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester:** A solution of 3-trifluoromethylbenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (332 mg, 1.0 mmol), as prepared in the preceding step, N-(tert-butoxycarbonyl)-4-piperidinemethanol (215 mg, 1.0 mmol), as prepared in step f of Example 1, and triphenylphosphine (263 mg, 1.0 mmol) in tetrahydrofuran (10 mL at 0°C was

treated with diethyl azodicarboxylate (175 mg, 1.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 3 h. Water (50 mL) was added. The reaction mixture was extracted into ethyl acetate (3 x 50 mL), washed sequentially with saturated NaHCO₃ (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 ethyl acetate:hexane) to give the title compound as a colorless liquid (375 mg, 70%). ¹H-NMR (300 MHz, CDCl₃) δ 1.26 (m, 2H), 1.47 (s, 9H), 1.77 (m, 2H), 1.89 (m, 1H), 2.24 (s, 3H), 2.73 (t, 2H), 3.67 (d, 2H), 4.13 (m, 2H), 6.34 (d, 1H), 6.36 (s, 1H), 6.62 (s, 1H), 7.72 (t, 1H), 7.94 (d, 1H), 8.09 (d, 2H).

d) 3-Trifluoromethylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]-methoxy]-5-methylphenyl ester acetic acid salt: 3-Trifluoromethylbenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (265 mg, 0.5 mmol), as prepared in the preceding step, was treated with 10 mL of 4 N HCl in 1,4-dioxane at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was concentrated from methylene chloride several times to give the amine salt. The amine salt was dissolved in DMF (10 mL) and treated with triethylamine (0.5 mL) and aminoiminomethanesulfonic acid (124 mg, 1.0 mmol). The reaction mixture was stirred at room temperature overnight. The DMF was removed *in vacuo*. The residue was dissolved in methylene chloride (200 mL). The organic phase was washed with 10% K₂CO₃ (2x50 mL), dried over K₂CO₃, and concentrated *in vacuo*. The residue was purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) to give the title compound as a colorless foam (123 mg, 47%). ¹H-NMR (300 MHz, CDCl₃) δ 1.44 (m, 2H), 1.79 (s, 3H), 1.94 (m, 2H), 2.09 (m, 1H), 2.22 (s, 3H), 3.10 (t, 2H), 3.71 (d, 2H), 4.08 (d, 2H), 6.33 (s, 1H), 6.37 (s, 1H), 6.60 (s, 1H), 7.28 (bs, 4H), 7.35 (t, 1H), 7.95 (d, 1H), 8.07 (d, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₁H₂₄N₃O₄SF₃: 472.2 (M+H), 494.1 (M+Na). Found: 472.6, 494.7.

Example 17

a) **Benzenesulfonic acid 3-benzyloxy-5-methylphenyl ester:** A solution of 3-benzyloxy-5-methylphenol (400 mg, 2.0 mmol), as prepared in step a of Example 3, in methylene chloride (10 mL) at 0°C was treated with N,N-diisopropylethylamine (0.4 mL) and benzenesulfonyl chloride (354 mg, 2.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 2 h. The reaction mixture was diluted with methylene chloride (200 mL) and water (50 mL). The organic extract was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 hexane:methylene chloride) to give the title compound as a colorless liquid (675 mg, 95%). ¹H-NMR(300 MHz, CDCl₃) δ 2.24 (s, 3H), 4.91 (s, 2H), 6.40 (t, 1H), 6.43 (s, 1H), 6.68 (s, 1H), 7.36 (m, 5H), 7.52 (t, 2H), 7.64 (d, 1H), 7.83 (t, 2H).

b) **Benzenesulfonic acid 3-hydroxy-5-methylphenyl ester:** A mixture of benzenesulfonic acid 3-benzyloxy-5-methylphenyl ester (532 mg, 1.5 mmol), as prepared in the preceding step, and 10% palladium on carbon (200 mg) in ethanol (20 mL) was hydrogenated (balloon) overnight. The catalyst was removed by filtering over diatomaceous earth and the filtrate was evaporated *in vacuo* to give the title compound as a colorless syrup (390 mg, 98%). ¹H-NMR (300 MHz, CDCl₃/CD₃OD) δ 2.19 (s, 3H), 6.27 (s, 1H), 6.54 (s, 1H), 6.66 (s, 1H), 7.43 (m, 1H), 7.55 (t, 1H), 7.70 (t, 1H), 7.85 (m, 2H).

c) **Benzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester:** To a solution of benzenesulfonic acid 3-hydroxy-5-methylphenyl ester (528 mg, 2.0 mmol), as prepared in the preceding step, N-(tert-butoxycarbonyl)-4-piperidinemethanol (430 mg, 2.0 mmol), as prepared in step f of Example 1, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at 0°C was added diethyl azodicarboxylate (349 mg, 2.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction mixture was diluted with methylene chloride (200 mL) and

water (50 mL). The organic extract was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 ethyl acetate:hexane) to give the title compound as a colorless liquid (781 mg, 84%).

5 ¹H-NMR (300 MHz, CDCl₃) δ 1.24 (m, 2H), 1.47 (s, 9H), 1.76 (m, 2H), 1.88 (m, 1H), 2.24 (s, 3H), 2.73 (t, 2H), 3.66 (d, 2H), 4.12 (m, 2H), 6.32 (s, 1H), 6.37 (s, 1H), 6.58 (s, 1H), 7.54 (t, 2H), 7.67 (t, 1H), 7.86 (d, 2H).

d) Benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt: Benzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (462 mg, 1.0 mmol), as prepared in the preceding step, was treated with 15 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and concentrated from methylene chloride several times to give the amine salt. This was dissolved in DMF (10 mL) and then treated with triethylamine (1.0 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol). The reaction mixture was stirred at room temperature overnight. The DMF was evaporated *in vacuo*. The residue was dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (3x50 mL), dried over K CQ and concentrated *in vacuo*. The residue was purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) and crystallized from acetonitrile-ethyl ether to give the title compound as white crystals (185 mg, 40%). ¹H-NMR (300 MHz, CD₃OD) δ 1.41 (m, 2H), 1.89 (s, 3H), 1.92 (m, 2H), 2.08 (m, 1H), 2.20 (s, 3H), 3.12 (dt, 2H), 3.75 (d, 2H), 3.91 (d, 2H), 6.35 (d, 2H), 6.67 (s, 1H), 7.61 (t, 2H), 7.75 (t, 1H), 7.83 (d, 2H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₅N₃O₄S: 404.2 (M+H). Found: 404.5.

10
15
20
25

Example 18

a) 3-Chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester:

Orcinol monohydrate (1.42 g, 10 mmol) and 3-chlorobenzenesulfonyl chloride (2.43 g, 11 mmol) were vigorously stirred in a mixture of saturated NaHCO₃ (30 mL) and ethyl ether (30 mL) at room temperature for 2 days. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic extract was washed sequentially with brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (2% ethyl acetate in methylene chloride) to give the title compound as a pale-yellow liquid (2.08 g, 69%). ¹H-NMR (300 MHz, CDCl₃) δ 2.24 (s, 3H), 5.32 (s, 1H), 6.33 (t, 1H), 6.140 (s, 1H), 6.57 (s, 1H), 7.48 (t, 1H), 7.65 (dt, 1H), 7.72 (dt, 1H), 7.86 (t, 1H).

b) 3-Chlorobenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester :

A solution of 3-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenol (600 mg, 2.0 mmol), as prepared in the preceding step, N-(tert-butoxycarbonyl)-4-piperidinemethanol (430 mg, 2.0 mmol), as prepared in step f of Example 1, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at 0°C was treated with diethyl azodicarboxylate (349 mg, 2.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic extract was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:3 ethyl acetate:hexane) to give the title compound as a colorless liquid (800 mg, 81%). ¹H-NMR (300 MHz, CDCl₃) δ 1.24 (m, 2H), 1.47 (s, 9H), 1.75 (m, 2H), 1.90 (m, 1H), 2.25 (s, 3H), 2.73 (t, 2H), 3.68 (d, 2H), 4.13 (m, 2H), 6.34 (t, 1H), 6.39 (s, 1H), 6.61 (s, 1H), 7.49 (t, 1H), 7.63 (d, 1H), 7.75 (d, 1H), 7.86 (t, 1H).

c) **3-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)-piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt:** 3-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (496 mg, 1.0 mmol), as prepared in the preceding step, was treated with 15 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and concentrated from methylene chloride several times to give the amine salt. This was dissolved in DMF (10 mL) and treated with triethylamine (1.0 mL) and aminoiminomethanesulfonic acid (248 mg, 2.0 mmol). The reaction mixture was stirred at room temperature overnight. The DMF was removed *in vacuo*. The residue was dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (3x50 mL), dried over K₂CO₃, and concentrated *in vacuo*. The residue was purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) and crystallized from acetonitrile/ethyl ether to give product the title compound as white crystals (305 mg, 61 %). ¹H-NMR (300 MHz, CD₃OD) δ 1.41 (m, 2H), 1.89 (s, 3H), 1.93 (m, 2H), 2.09 (m, 1H), 2.23 (s, 3H), 3.12 (dt, 2H), 3.77 (d, 2H), 3.92 (d, 2H), 6.38 (d, 2H), 6.70 (s, 1H), 7.61 (t, 1H), 7.77 (t, 1H), 7.80 (s, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₄N₃O₄SCl:438.1 (M+H). Found: 438.9.

The following additional compounds (Examples 19-35) were synthesized by a process analogous to that employed in Example 18:

Example 19

3-Methoxybenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: ¹H-NMR (300 MHz, DMSO-d₆) δ 1.17-1.28 (m, 2 H), 1.74-1.79 (m, 2 H), 1.98 (m, 1 H), 2.21 (s, 3 H), 3.02 (br t, 2 H), 3.75 (d, 2 H), 3.84-3.88 (m, 5 H), 6.39 (br s, 1 H), 6.47 (br s, 1 H), 6.74 (br s, 1 H), and 7.37-7.62 (m, 4 H). Mass spectrum (MALDI-TOF, α-cyano-4-

-77-

hydroxycinnamic acid matrix) calcd. for $C_{21}H_{27}N_3O_5S$: 434.2 (M + H). Found: 434.7.

Example 20

5 *3-[(Carboxy)methoxy]benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester*: 1H -NMR (300 MHz, $CDCl_3$ /TFA) δ 1.37-1.52 (m, 2 H), 1.96-2.10 (m, 3 H), 2.25 (s, 3 H), 3.14 (br t, 2 H), 3.75-3.86 (m, 4 H), 4.79 (s, 2 H), 6.36 (br s, 1 H), 6.40 (br s, 1 H), 6.62 (br s, 1 H), and 7.28-7.56 (m, 4 H). Mass spectrum (MALDI-TOF, α -cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{22}H_{27}N_3O_7S$: 478.2 (M + H),
10 500.1 (M + Na). Found: 478.1, 500.1.

Example 21

15 *3-Hydroxybenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride*: 1H -NMR (300 MHz, $DMSO-d_6$) δ 1.20-1.29 (m, 2 H), 1.77 (br d, 2 H), 1.99 (s, 1 H), 2.22 (s, 3 H), 3.02 (t, 2 H), 3.76 (d, 2 H), 3.87 (m, 2 H), 6.35 (br s, 1 H), 6.44 (br s, 1 H), 6.74 (br s, 1 H), and 7.17-7.51 (m, 4 H). Mass spectrum (MALDI-TOF, α -cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{20}H_{25}N_3O_5S$: 420.2 (M + H), 442.1 (M + Na). Found: 420.2, 442.1.

Example 22

20 *3-(2'-Hydroxyethoxy)benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride*: 1H -NMR (300 MHz, $DMSO-d_6$) δ 1.20-1.28 (m, 2 H), 1.77 (br d, 2 H), 1.98 (m, 1 H), 2.21 (s, 3 H), 3.02 (t, 2 H), 3.69-3.88 (m, 6 H), 4.07 (t, 2

-78-

H), 4.94 (t, 1 H), 6.40 (br s, 1 H), 6.47 (br s, 1 H), 6.74 (br s, 1 H), and 7.30-7.61 (m, 4 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{22}H_{29}N_3O_6S$: 464.2 (M + H). Found: 464.4.

Example 23

5 *3-(2',3'-Dihydroxypropoxy)benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride*: 1H -NMR (300 MHz, DMSO- d_6) δ 1.25-1.42 (m, 2 H), 1.83-2.07 (m, 3 H), 2.23 (s, 3 H), 2.8-3.1 (m, 2 H), 3.26 (br d, 1 H), 3.47 (d, 2 H), 3.74-3.98 (m, 5-6 H), 6.38 (br t, 1 H), 6.47 (br s, 1 H), 6.73 (br s, 1 H), and 7.33-7.60 (m, 10 4 H). Mass spectrum (MALDI-TOF, α -cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{23}H_{31}N_3O_7S$: 494.2 (M + H). Found: 494.1.

Example 24

15 *2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-chlorophenyl ester hydrochloride*: 1H -NMR (300 MHz, DMSO- d_6) δ 1.24 (m, 2 H), 1.75 (d, J = 11.3 Hz, 2 H), 1.99 (m, 1 H), 3.01 (t, J = 12 Hz, 2 H), 3.86 (m, 4 H), 6.65 (t, J = 2.2 Hz, 1 H), 6.74 (t, J = 2.1 Hz, 1 H), 7.07 (t, J = 2.1 Hz, 1 H), 7.47 (br s, 3 H), 7.61 (t, J = 7.4 Hz, 1 H), 7.89 (m, 2 H), 7.99 (d, J = 15.6 Hz, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{19}H_{21}Cl_2N_3O_4S$: 458.1 (M + H); Found: 457.9.

20

Example 25

3-Nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: 1H -NMR (300 MHz, DMSO- d_6) δ 1.24 (m, 2 H), 1.76 (d, J = 12.5 Hz, 2 H), 1.99 (m, 1 H), 2.22 (s, 3 H), 3.01

-79-

(t, J = 12.1 Hz, 2 H), 3.76 (d, J = 7.0 Hz, 2 H), 3.88 (d, J = 13.2 Hz, 2 H), 6.49 (s, 1 H), 6.52 (s, 1 H), 6.77 (s, 1 H), 7.45 (br s, 3 H), 7.98 (t, J = 8.0 Hz, 1 H), 8.30 (d, J = 8.0 Hz, 1 H), 8.50 (s, 1 H), 8.65 (d, J = 8.1 Hz, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{20}H_{24}N_4O_6S$: 449.1 (M + H), 471.1 (M + Na); Found: 449.2, 471.3.

Example 26

3-Aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: 1H -NMR (300 MHz, DMSO- d_6) δ 1.25 (m, 2 H), 1.76 (d, J = 13.0 Hz, 2 H), 1.98 (m, 1 H), 2.22 (s, 3 H), 3.01 (t, J = 12.1 Hz, 2 H), 3.75 (d, J = 6.2 Hz, 2 H), 3.88 (d, J = 13.2 Hz, 2 H), 5.79 (br s, 2 H), 6.31 (s, 1 H), 6.45 (s, 1 H), 6.72 (s, 1 H), 6.89 (s, 1 H), 6.91 (s, 1 H), 7.03 (s, 1 H), 7.27 (t, J = 7.9 Hz, 1 H), 7.45 (br s, 3 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{20}H_{26}N_4O_4S$: 419.2 (M + H); Found: 419.6.

Example 27

2-(Methoxycarbonyl)benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: 1H -NMR (300 MHz, DMSO- d_6) δ 1.25 (m, 2 H), 1.90 (d, J = 12.5 Hz, 2 H), 2.01 (m, 1 H), 2.23 (s, 3 H), 3.06 (t, J = 12.5 Hz, 2 H), 3.69 (d, J = 7.6 Hz, 2 H), 3.97 (s, 1 H), 4.08 (d, J = 12.0 Hz, 2 H), 6.46 (s, 1 H), 6.51 (s, 1 H), 6.58 (s, 1 H), 7.30 (br s, 3 H), 7.58 (m, 1 H), 8.71 (d, J = 7.4 Hz, 2 H), 7.86 (d, J = 7.7 Hz, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{22}H_{27}N_3O_6S$: 462.2 (M + H), 484.2 (M + Na); Found: 462.2, 484.5.

Example 28

4-Nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: ¹H-NMR (300 MHz, DMSO-d₆) δ 1.25 (m, 2 H), 1.76 (d, J = 13.0 Hz, 2 H), 1.99 (m, 1 H), 2.22 (s, 3 H), 3.01 (t, J = 12.2 Hz, 2 H), 3.76 (d, J = 6.0 Hz, 2 H), 3.88 (d, J = 13.0 Hz, 2 H), 6.46 (s, 1 H), 6.49 (s, 1 H), 6.77 (s, 1 H), 7.42 (br s, 3 H), 8.18 (d, J = 8.1 Hz, 2 H), 8.46 (d, J = 8.1 Hz, 2 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₄N₄O₆S: 449.1 (M + H); Found: 448.9.

Example 29

4-Aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: ¹H-NMR (300 MHz, DMSO-d₆) δ 1.25 (m, 2 H), 1.77 (d, J = 12.7 Hz, 2 H), 1.98 (m, 1 H), 2.21 (s, 3 H), 3.01 (t, J = 12.3 Hz, 2 H), 3.74 (d, J = 6.2 Hz, 2 H), 3.88 (d, J = 13.8 Hz, 2 H), 6.28 (s, 1 H), 6.41 (s, 3 H), 6.61 (s, 1 H), 6.64 (s, 1 H), 6.69 (s, 1 H), 7.41 (bs, 6 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₆N₄O₄S: 419.1 (M + H); Found: 419.1.

Example 30

2-Nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: ¹H-NMR (300 MHz, DMSO-d₆) δ 1.25 (m, 2 H), 1.77 (d, J = 12.7 Hz, 2 H), 2.00 (m, 1 H), 2.23 (s, 3 H), 3.01 (t, J = 12.4 Hz, 2 H), 3.79 (d, J = 6.1 Hz, 2 H), 3.89 (d, J = 13.2 Hz, 2 H), 6.51 (s, 1 H), 6.55 (s, 1 H), 6.80 (s, 1 H), 7.48 (br s, 3 H), 7.91 (t, J = 7.6 Hz, 1 H), 8.06 (m, 2 H), 8.21 (d, J = 7.4 Hz, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₄N₄O₆S: 449.1 (M + H); Found: 449.0.

Example 31

2-Aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: ¹H-NMR (300 MHz, DMSO-d₆) δ 1.23 (m, 2 H), 1.76 (d, J = 13.3 Hz, 2 H), 1.98 (m, 1 H), 2.20 (s, 3 H), 3.01 (t, J = 12.2 Hz, 2 H), 3.73 (d, J = 6.2 Hz, 2 H), 3.87 (d, J = 13.5 Hz, 2 H), 6.25 (br s, 2 H), 6.35 (s, 1 H), 6.47 (s, 1 H), 6.58 (t, J = 7.5 Hz, 1 H), 6.71 (s, 1 H), 6.94 (d, J = 8.0 Hz, 1 H), 7.34 (t, J = 8.3 Hz, 1 H), 7.40 (br s, 3 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₆N₄O₄S: 419.2 (M + H), 441.2 (M + Na); Found: 419.1, 441.2.

Example 32

2-Chloro-3-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride: ¹H-NMR (300 MHz, DMSO-d₆) δ 1.25 (m, 2 H), 1.77 (d, J = 11.3 Hz, 2 H), 2.00 (m, 1 H), 2.23 (s, 3 H), 3.02 (t, J = 11.8 Hz, 2 H), 3.77 (d, J = 6.2 Hz, 2 H), 3.87 (d, J = 13.8 Hz, 2 H), 6.48 (s, 1 H), 6.56 (s, 1 H), 6.78 (s, 1 H), 7.35 (br s, 4 H), 7.83 (t, J = 8.1 Hz, 1 H), 8.24 (d, J = 8.0 Hz, 1 H), 8.47 (d, J = 8.2 Hz, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₃ClN₄O₆S: 483.1 (M + H); Found: 483.0.

Example 33

3-Amino-2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester dihydrochloride: ¹H-NMR (300 MHz, DMSO-d₆) δ 1.24 (m, 2 H), 1.76 (d, J = 11.3 Hz, 2 H), 1.99 (m, 1 H), 2.21 (s, 3 H), 3.01 (t, J = 12.6 Hz, 2 H), 3.76 (d, J = 6.0 Hz, 2 H), 3.86 (d, J = 13.0 Hz, 2 H), 6.40 (br s, 2 H), 6.49 (s, 1 H), 6.73 (s,

1 H), 7.08 (m, 1 H), 7.18 (m, 2 H), 7.38 (br s, 4 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{20}H_{25}ClN_4O_4S$: 453.1 (M + H); Found: 453.4.

Example 34

5 *2-Chlorobenzenesulfonic acid 5-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-2-(ethoxycarbonyl)-3-methylphenyl ester hydrochloride*: 1H -NMR (300 MHz, DMSO- d_6) δ 1.14-1.28 (m, 5 H), 1.74 (d, J = 12.96 Hz, 2 H), 1.91-1.99 (m, 1 H), 2.29 (s, 3 H), 3.00 (t, J = 12.02 Hz, 2 H), 3.78 (d, J = 6.2 Hz, 2 H), 3.88 (d, J = 13.6 Hz, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 6.29 (d, J = 2.3 Hz, 1 H),
10 6.90 (d, J = 2.1 Hz, 1 H), 7.46 (broad s, 3 H), 7.59-7.64 (m, 1 H), 7.82-7.97 (m, 3 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{23}H_{28}N_3O_6ClS$: 510.1 (M + H). Found: 510.4.

Example 35

15 *2-Chlorobenzenesulfonic acid 1-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester acetic acid salt*: 1H -NMR (300 MHz, DMSO- d_6) δ 7.75 - 8.1 (m, 5 H), 7.51 - 7.59 (m, 3 H), 7.19 (d, 1 H), 6.67 (d, 1 H), 3.83 - 3.93 (m, 24 H), 3.00 (t, 2 H), 2.14 (br, 1 H), 1.86 (d, 2 H), 1.64 (s, 3 H), and 1.28 - 1.39 (m, 2 H). Mass spectrum (MALDI-TOF; α -cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{18}H_{23}ClN_4O_3S$: 474.1 (M + H). Found:
20 473.8.

Example 36

a) *2-Chlorobenzenesulfonic acid 3-hydroxy-5-methoxyphenyl ester*:

The compound was produced by the method of step a of Example 7 from 5-

methoxyresorcinol to give 2.61 g (83% yield) of a crystalline solid after column chromatography. ¹H-NMR (CDCl₃; 300 MHz): δ 3.67 (s, 3H), 5.73 (s, 1H), 6.25-6.29 (m, 3H), 7.35-7.43 (m, 1H), 7.55-7.63 (m, 2H), 7.97 (dd, 1H).

5 **b) 2-Chlorobenzenesulfonic acid 3-[[1-N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methoxyphenyl ester:** The compound was produced by the method of step b of Example 7 using the compound of the preceding step to give 1.71 g (81% yield) of a crystalline solid after column chromatography. ¹H-NMR (CDCl₃; 300 MHz): δ 1.15-1.30 (m, 2H), 1.46 (s, 9H), 1.71-2.0 (m, 3H), 2.72 (t, 2H), 3.68 (s and d, 5H), 4.1-4.24 (m, 2H), 6.24-6.3 (m, 3H), 7.36-7.42 (m, 1H), 7.55-7.64 (m, 2H), 7.97 (dd, 1H).

10 **c) 2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methoxyphenyl ester:** The compound of the preceding step (1.8 g, 3.52 mmol) was treated with 25 mL of 25% trifluoroacetic acid in methylene chloride at ambient temperature for 15 min. The solvent was evaporated, the residue was azeotroped with acetonitrile (3 times), and placed under high vacuum. The residue was dissolved in methanol (30 mL) and treated with 1*H*-pyrazole-1-carboxamidinium hydrochloride (1.03 g, 7.04 mmol) and triethylamine (1.39 mL, 10.5 mmol). The reaction mixture was stirred at ambient temperature overnight. The solvent was evaporated to dryness.

15 The residue was placed under high vacuum, then treated with ethyl acetate and water. Upon shaking, a crystalline precipitate was produced, which was collected by filtration, and dried under high vacuum to give white solid. ¹H-NMR (DMSO-d₆; 300 MHz): δ 1.25 (t, 2H), 1.76 (d, 2H), 2.0 (m, 1H), 3.03 (q, 2H), 3.65 (s, 3H), 3.77 (d, 2H), 3.86 (d, 2H), 6.16 (s, 1H), 6.25 (s, 1H), 6.47 (s, 1H), 7.35 (s, 4H), 7.59 (t, 1H), 7.8-7.98 (m, 3H). Mass spectrum (MALDI-TOF) calcd. for C₂₀H₂₄N₃O₅SCl: 454.1 (M+H). Found 454.0.

20

25

Example 37

a) 2-Chlorobenzenesulfonic acid 3-hydroxy-4-ethoxycarbonyl-5-

methylphenyl ester: Ethyl 2,4-dihydroxy-6-methylbenzoate (1 g, 5 mmol) was dissolved in anhydrous methylene chloride (5 mL) and cooled in an ice bath. To this solution was added 2-chlorobenzenesulfonyl chloride (1.1 g, 5.2 mmol) and N,N-diisopropylethylamine (0.89 mL, 5.1 mmol). The mixture was stirred for 3 h under a nitrogen atmosphere. The reaction mixture was diluted with methylene chloride and washed sequentially with 10% HCl, aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, and concentrated *in vacuo* to give a white solid. Recrystallization from cold hexane to give 1.67 g of a white solid (90%). ¹H-NMR (DMSO-d₆; 300 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 2.15 (s, 3H), 4.25 (q, J = 7.1 Hz, 2H), 6.49-6.52 (m, 2H), 7.57-7.63 (m, 1H), 7.57-7.63 (m, 2H), 7.81-7.99 (m, 1H), 10.41 (s, 1H).

b) 2-Chlorobenzenesulfonic acid 3-[[1-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-4-ethoxycarbonyl-5-methylphenyl

ester: A solution of 2-chlorobenzenesulfonic acid 3-hydroxy-4-ethoxycarbonyl-5-methylphenyl ester (830 mg, 2.2 mmol), as prepared in the preceding step, N-(tert-butoxycarbonyl)-4-piperidinemethanol (483 mg, 2.2 mmol), as prepared in step f of Example 1, and triphenylphosphine (589 mg, 2.2 mmol) in tetrahydrofuran (15 mL) at 0°C was treated with diethyl azodicarboxylate (390 mg, 2.2 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature overnight. The solvent was removed under vacuum and the residue was purified by flash column chromatography (1:3 ethyl acetate:hexane) to give 1.1 g (86 %) of the title compound as an oil. ¹H-NMR (CDCl₃; 300 MHz): δ 1.16-1.29 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.46 (s, 9H), 1.69-1.74 (m, 2H), 1.83-1.92 (m, 1H), 2.2 (s, 3H), 2.66-2.74 (m, 2H), 3.71 (d, J = 6.2 Hz, 2H), 4.09-4.16 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 6.53-6.56 (m, 2H), 7.38-7.43 (m, 1H), 7.57-7.65 (m, 2H), 7.94-7.98 (m, 1H).

c) **2-Chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]-4-ethoxycarbonyl-5-methylphenyl ester hydrochloride:**

2-Chlorobenzenesulfonic acid 3-[[1-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-4-ethoxycarbonyl-5-methylphenyl ester (800 mg, 1.44 mmol), as prepared in the preceding step, was treated with 4 N dioxane in HCl for 3 h at which time ether was added to the mixture in order to precipitate the HCl salt. The precipitated solid was collected by filtration and washed with ether. Drying under vacuum gave 653 mg (90 %) of a white solid. ¹H-NMR (CDCl₃/CD₃OD; 300 MHz): δ 1.35 (t, J = 7.1 Hz, 3H), 1.60-1.72 (m, 2H), 2.02-2.06 (m, 3H), 2.2 (s, 3H), 2.89-2.98 (m, 2H), 3.45-3.49 (m, 2H), 3.79 (d, J = 6.0 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 6.56-6.59 (m, 2H), 7.37-7.49 (m, 1H), 7.63-7.69 (m, 2H), 7.96-7.99 (m, 1H). Mass spectrum (MALDI-TOF) calcd. for C₂₂H₂₆NO₆ClS: 468.1 (M+H). Found 468.2.

d) **2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-4-ethoxycarbonyl-5-methylphenyl ester hydrochloride:**

2-Chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]-4-ethoxycarbonyl-5-methylphenyl ester hydrochloride (0.18 mmol), as prepared in the preceding step, was dissolved in anhydrous DMF and treated with 1*H*-pyrazole-1-carboxamidinium hydrochloride (57.5 mg, 0.39 mmol) and triethylamine (TEA) (135 µL, 0.96 mmol). This mixture was stirred for 1 day at which time more 1*H*-pyrazole-1-carboxamidinium hydrochloride (29 mg) and TEA (67 µL) were added and the mixture was stirred for another day. The solvent was evaporated and the residue was dissolved in methylene chloride and washed with ice water. The methylene chloride layer was separated, dried over MgSO₄ and evaporated to give an oil. This oil was crystallized from methanol/ether. The solid was separated and triturated 3 times with hot ether to give a white solid, 55 mg (60 %). ¹H-NMR (CDCl₃/CD₃OD; 300 MHz): δ 1.33-1.46 (m, 5H), 1.87-1.91 (m, 2H), 2.0-2.07 (m, 1H), 2.2 (s, 3H), 2.99-3.07 (m, 2H), 3.78 (d, J = 6.0 Hz, 2H), 3.9-4.0 (m, 2H), 4.35 (q, J = 7.1 Hz, 2H), 6.55-6.61 (m, 2H), 7.39-7.50 (m,

1H), 7.63-7.69 (m, 2H), 7.96-7.99 (m, 1H). Mass spectrum (MALDI-TOF) calcd. for $C_{23}H_{28}N_3O_6ClS$: 510.1 (M+H). Found 510.1.

Example 38

5 **a) 1-Benzyloxy-3-[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy-5-methylbenzene:** A solution of 3-benzyloxy-5-methylphenol (2.0 g, 10 mmol), as prepared in step a of Example 3, N-(tert-butoxycarbonyl)-4-piperidinemethanol (2.15 g, 10 mmol), as prepared in step f of Example 1, and triphenylphosphine (2.62 g, 10 mmol) in tetrahydrofuran (40 mL) at 0°C was treated with diethyl azodicarboxylate (1.74 g, 10 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic extract was washed sequentially with saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:3 ethyl acetate:hexane) to give the title compound as a colorless liquid (1.95 g, 47%). 1H -NMR (300 MHz, $CDCl_3$): δ 1.26 (m, 2H), 1.46 (s, 9H), 1.80 (d, 2H), 1.92 (m, 1H), 2.29 (s, 3H), 2.74 (t, 2H), 3.76 (d, 2H), 4.12 (m, 2H), 6.34 (s, 1H), 6.35 (s, 1H), 6.42 (s, 1H), 7.41 (m, 5H).

15 **b) 3-[N-(tert-Butoxycarbonyl)piperidin-4-yl]methoxy-5-methylphenol:** 1-Benzyloxy-3-[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy-5-methylbenzene (1.65 g, 4.0 mmol), as prepared in the preceding step, in ethanol (50 mL) containing 10% palladium on carbon (200 mg) was hydrogenated (balloon) for 3 h. The catalyst was removed by filtration through diatomaceous earth (methanol washes) and the filtrate was concentrated *in vacuo* to give the title compound as as white solid (1.18 g, 92%). 1H -NMR (300 MHz, $CDCl_3$): δ 1.25 (m, 2H), 1.47 (s, 9H), 1.80 (d, 2H), 1.93 (m, 1H), 2.26 (s, 3H), 2.75 (t, 2H), 3.74 (d, 2H), 4.13 (m, 2H), 5.57 (s, 1H), 6.22 (t, 1H), 6.27 (dd, 2H).

c) **2-Trifluoromethylbenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester:** A solution of 3-[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy-5-methylphenol (321 mg, 1.0 mmol), as prepared in the preceding step, in methylene chloride (15 mL) at 0°C was treated with N,N-diisopropylethylamine (0.5 mL) and 2-trifluoromethylbenzenesulfonyl chloride (245 mg, 1.0 mmol). The reaction mixture was stirred at 0°C for 3 h. Ethyl acetate (150 mL) was added and the reaction mixture was washed with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (methylene chloride) to give the title compound as a yellow liquid (490 mg, 92%). ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (m, 2H), 1.47 (s, 9H), 1.77 (m, 2H), 1.89 (m, 1H), 2.25 (s, 3H), 2.73 (t, 2H), 3.69 (d, 2H), 4.13 (m, 2H), 6.44 (t, 1H), 6.46 (s, 1H), 6.60 (s, 1H), 7.70 (t, 1H), 7.80 (t, 1H), 7.99 (d, 1H), 8.13 (d, 1H).

d) **2-Trifluoromethylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt:** 2-Trifluoromethylbenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (370 mg, 0.7 mmol), as prepared in the preceding step, was treated with 10 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and then concentrated from methylene chloride several times to give the amine salt. This was then dissolved in DMF (10 mL) and treated with triethylamine (0.4 mL) and aminoiminomethanesulfonic acid (186 mg, 1.5 mmol). The reaction mixture was stirred at room temperature overnight. The DMF was removed *in vacuo* and the residue was then dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (3 x 50 mL), dried over K₂CO₃ and concentrated *in vacuo*. The residue was purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) and crystallized from acetonitrile-ethyl ether to give the title compound as a white solid (270 mg, 72 %). ¹H-NMR (300 MHz, CD₃OD): δ 1.42 (m, 2H), 1.90 (s, 3H), 1.94 (m, 2H), 2.10 (m, 1H), 2.22 (s, 3H),

3.12 (dt, 2H), 3.79 (d, 2H), 3.85 (d, 2H), 6.39 (s, 1H), 6.43 (t, 1H), 6.70 (s, 1H), 7.81 (t, 1H), 7.94 (t, 1H), 8.09 (d, 2H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{21}H_{24}N_3O_4SF_3$: 472.2 ($M+H^+$), 494.1 ($M+Na^+$). Found: 472.7, 494.6.

5

Example 39

a) 3-Methylbenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester: A solution of 3-[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy-5-methylphenol (321 mg, 1.0 mmol), as prepared in step b of Example 20, in methylene chloride (15 mL) at 0°C was treated with N,N-diisopropylethylamine (0.5 mL) and 3-methylbenzenesulfonyl chloride (191 mg, 1.0 mmol). The reaction mixture was stirred at 0°C for 3 h. The reaction mixture was extracted with ethyl acetate (3 x 50 mL), washed sequentially with saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography (methylene chloride) to give the title compound as a yellow oil (425 mg, 89%). 1H -NMR (300 MHz, $CDCl_3$): δ 1.24 (m, 2H), 1.47 (s, 9H), 1.76 (m, 2H), 1.89 (m, 1H), 2.24 (s, 3H), 2.43 (t, 3H), 2.73 (t, 2H), 3.66 (d, 2H), 4.13 (m, 2H), 6.33 (t, 1H), 6.38 (s, 1H), 6.59 (s, 1H), 7.44 (dt, 2H), 7.65 (dd, 2H).

b) 3-Methylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt: 3-Methylbenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (380 mg, 0.8 mmol), as prepared in the preceding step, was treated with 10 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and concentrated from methylene chloride several times to give the amine salt. This was then dissolved in DMF (10 mL) and treated with triethylamine (0.5 mL) and aminoiminomethanesulfonic acid (200 mg, 1.6 mmol). The reaction mixture was

stirred at room temperature overnight. The DMF was removed *in vacuo*. The residue was dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (3x50 mL), dried over K₂CO₃ and concentrated *in vacuo*. The residue was purified by flash column chromatography (88:10:2 methylene chloride:methanol:acetic acid) and crystallized from acetonitrile/ethyl ether to give the title compound as a white solid (295 mg, 76 %). ¹H-NMR (300 MHz, CD₃OD): δ 1.41 (m, 2H), 1.89 (s, 3H), 1.92 (m, 2H), 2.08 (m, 1H), 2.21 (s, 3H), 2.42 (s, 3H), 3.12 (dt, 2H), 3.76 (d, 2H), 3.92 (d, 2H), 6.35 (d, 2H), 6.67 (s, 1H), 7.48 (t, 1H), 7.60 (m, 3H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₁H₂₇N₃O₄S: 418.2 (M+H), 440.2 (M+Na). Found: 418.4, 440.6.

Example 40

a) 3,5-Dibenzyloxybenzaldehyde: To a solution of 2.39 g (17.3 mmol) of 3,5-dihydroxybenzaldehyde in 10 mL of DMF at 0°C under a nitrogen atmosphere was added slowly 831 mg (34.6 mmol) of NaH (100%). After hydrogen evolution had ceased, 5.4 mL (37 mmol) of benzyl bromide was added. The ice bath was removed and the reaction mixture was stirred to room temperature for 1 h. The reaction mixture was quenched and acidified with aqueous HCl, extracted into ether, and washed with 1 N NaOH followed by a washing with 1 N HCl. The organic extract was dried (MgSO₄) and the product was purified by flash chromatography (20 to 30% ether/hexane) to give 3.28 g (60% yield) of the title compound as a colorless solid. ¹H-NMR (300 MHz, CDCl₃) δ 9.90 (s, 1 H), 7.3-7.5 (m, 10 H), 7.11 (d, 2 H, J = 2 Hz), 6.87 (t, 1H, J = 2 Hz), and 5.09 (s, 4 H).

b) 5-Vinylresorcinol dibenzylether: To 2.3 g (6.43 mmol) of methyltriphenylphosphonium bromide in 15 mL of anhydrous DMSO at ambient temperature was added 160 mg (6.7 mmol) of NaH. The reaction mixture was stirred for 40 min. To the resulting yellow suspension was added 1.8 g (5.84 mmol) of 3,5-dibenzyloxybenzaldehyde, as prepared in the preceding step.

Tetrahydrofuran (5 mL) was added to the reaction mixture. After 10 min, a colorless suspension resulted. The reaction was stirred for 30 min, quenched with 5% aqueous citric acid, extracted into ethyl acetate/tetrahydrofuran, washed with 4 x 50 mL H₂O, dried (MgSO₄), and concentrated *in vacuo*. The product was purified by flash chromatography (methylene chloride/hexane (1:4 to 1:3)) to give 1.65 g (81% yield) of the title compound. ¹H-NMR (300 MHz, CDCl₃) δ 7.2 - 7.45 (m, 10H), 6.67 (d, 1 H, J = 2 Hz), 6.63 (dd, 1 H, J = 11, 17 Hz), 6.54 (t, 1 H, J = 2 Hz), 5.70 (d, 1 H, J = 11 Hz), 5.24 (d, 1H, J = 17 Hz), 5.04 (s, 4 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for C₂₂H₂₀O₂: 317.2 (M+H), 339.1 (M+Na). Found: 317.6, 339.0

c) 5-Ethylresorcinol: A mixture of 1.07 g (3.39 mmol) of 5-vinylresorcinol dibenzylether, as prepared in the preceding step, and 200 mg of 10% Pd/C in 20 mL of ethanol was hydrogenated at atmospheric pressure and ambient temperature for 14 h. The reaction mixture was filtered through diatomaceous earth (ethanol rinse) and concentrated to give 511 mg of the crude title compound which was used as is in the next reaction. ¹H-NMR (300 MHz, CDCl₃): δ 6.27 (dd, 1 H, J = 0.4, 2.2 Hz), 6.18 (t, 2 H), 2.53 (q, 2 H), 1.19 (t, 3 H). Mass spectrum (MALDI-TOF; sinapinic acid matrix) calcd. for C₈H₁₀O₂: 139.1 (M+H). Found: 139.5.

d) 2-Chlorobenzenesulfonic acid 3-hydroxy-5-ethylphenyl ester: A biphasic mixture of 298 mg (2.25 mmol) of 5-ethylresorcinol, as prepared in the preceding step, 714 mg (3.38 mmol) of 2-chlorobenzenesulfonyl chloride in 10 mL of ether and 10 mL of saturated NaHCO₃ was vigorously stirred for 3 days. The reaction mixture was extracted into a mixture of ethyl acetate/ether, washed with saturated NaHCO₃, and dried (MgSO₄). Concentration *in vacuo* and purification by flash chromatography (methylene chloride:ether (98:2 to 95:5)) gave 324 mg (47% yield) of the title compound as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.95 (dd, 1 H, J = 2, 7 Hz), 7.55-7.64 (m, 2 H), 7.34-7.40 (m, 1H), 6.56 (m, 1 H), 6.51 (m, 1 H), 6.47 (t, 1H), 5.22 (bs, 1H), 2.50 (q, 2H), 1.26

(t, 3H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{14}H_{13}ClO_4S$: 335.0 (M + Na). Found: 334.9.

e) **2-Chlorobenzenesulfonic acid 3-[1-N-(tert-butoxycarbonyl)-piperidin-4-yl]-5-ethylphenyl ester:** To a solution of 324 mg (1.06 mmol) of 2-chlorobenzenesulfonic acid 3-hydroxy-5-ethylphenyl ester, as prepared in the preceding step, in 5 mL of tetrahydrofuran containing 314 mg (1.46 mmol) of N-tert-butoxycarbonyl-4-piperidinemethanol, as prepared in step f of Example 1, 400 μ L (3.6 mmol) of N-methylmorpholine, and 416 mg (2.53 mmol) of triphenylphosphine was added 250 μ L (1.59 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at ambient temperature for 14 h, quenched with H_2O , and extracted into ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (ether:methylene chloride 1:99) gave 427 mg (80% yield) of the title compound as a colorless oil. 1H -NMR (300 MHz, $CDCl_3$): δ 7.96 (dd, 1H, J = 1, 7 Hz), 7.55-7.64 (m, 2 H), 7.34-7.40 (m, 1 H), 6.59 (m, 1H), 6.49 - 6.56 (m, 2 H), 4.13 (br, 2 H), 3.69 (d, 1H, J = 6 Hz), 2.73 (t, 2 H, J = 12 Hz), 2.51 (q, 2 H), 1.84 - 1.95 (m, 1H), 1.77 (br d, 2 H), 1.46 (s, 9 H), 1.21 (t, 3 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{25}H_{32}ClNO_6S$: 532.2 (M + Na). Found: 532.5, 410.1 (M - (tert-butoxycarbonyl) + H).

f) **2-Chlorobenzenesulfonic acid 3-[[piperidin-4-yl]methoxy]-5-ethylphenyl ester hydrochloride:** A solution of 420 mg (0.834 mmol) of 2-chlorobenzenesulfonic acid 3-[1-N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-ethylphenyl ester, as prepared in the preceding step, in 2 mL of methylene chloride was treated with 2 mL of 4 N HCl in dioxane. The reaction mixture was stirred for 1 h at ambient temperature and then concentrated repeatedly from ether/methylene chloride to provide 373 mg (91% yield) of the title compound as a foam. 1H -NMR (300 MHz, $CDCl_3$): δ 9.72 (bs, 1 H), 9.42 (bs, 1 H), 7.96 (dd, 1H, J = 1, 7 Hz), 7.57-7.66 (m, 2 H), 7.35-7.41 (m, 1 H), 6.59 (s, 1 H), 6.52 (s, 1 H), 6.49 (t, 1 H), 3.74 (d, 2 H, J = 5 Hz), 3.57 (d, 2 H, J = 11 Hz), 2.92 (br, 2 H), 2.52 (q, 2 H), 2.05 (br d, 2 H), 1.80 (br t, 2 H), 1.10 (t, 3 H).

Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{20}H_{24}ClNO_4S$: 410.1 (M + H), 432.1 (M + Na). Found: 410.6, 432.6.

g) 2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-ethylphenyl ester

5 **hydrochloride:** 2-Chlorobenzenesulfonic acid 3-[[piperidin-4-yl]methoxy]-5-ethylphenyl ester hydrochloride (313 mg), as prepared in the preceding step, was dissolved in methylene chloride (20 mL) and washed with saturated $NaHCO_3$ (20 mL), dried (K_2CO_3), and concentrated to provide the free base (307 mg) as an oil. This was diluted with 2 mL of DMF and then treated with 680 μ L (6.18 mmol)

10 of N,N-diisopropylethylamine, and 227 mg (1.55 mmol) of 1H-pyrazole-1-carboxamide hydrochloride. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was quenched with saturated Na_2CO_3 , then 1 N NaOH, extracted into methylene chloride/tetrahydrofuran, dried (K_2CO_3) and concentrated. The residue was dissolved in a minimal amount of

15 methylene chloride, treated with 2 mL of 4 N HCl in dioxane and concentrated. Silica gel chromatography (10 g Water's Associates Silica gel Sep Pak SPE column) with elutions of methylene chloride: methanol (4:1) did not remove fully pyrazole contamination. Purification of 75 mg of the crude material was accomplished by preparative (two 1000 micron plates, 20 x 20 cm) silica gel thin

20 layer chromatography (methylene chloride:methanol (4:1)) to provide pure product. To insure complete HCl salt formation, the material was dissolved in methylene chloride and treated with 500 μ L of 4 N HCl in dioxane. Repeated concentrations from toluene/methylene chloride provided the title compound (65 mg) as a white powder. 1H -NMR (300 MHz, $CDCl_3$): δ 7.95 (d, 1H), 7.57 - 7.65

25 (m, 2 H), 7.33-7.41 (m, 1H), 6.59 (s, 1H), 6.48-6.50 (m, 2 H), 4.04 (br s, 2 H), 3.72 (d, 2 H, J = 3 Hz), 3.09 (br s, 3 H), 2.50 (q, 2 H), 1.93-2.09 (m, 3 H), 1.09 (t, 3 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{22}H_{26}ClN_3O_4S$: 452.1 (M + H, ^{35}Cl) and 454.1 (M + H, ^{37}Cl). Found: 452.5 and 454.6.

Example 41

a) **2-Chlorobenzenesulfonic acid 3-[[5-(N-tert-butoxycarbonyl)amino]pentoxy]-5-methylphenyl ester:** A solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (600 mg, 2.0 mmol),
5 as prepared in step c of Example 3, N-(tert-butoxycarbonyl)-5-aminopentanol (426 mg, 2.0 mmol) and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at 0°C was treated with diethyl azodicarboxylate (349 mg, 2.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 3 h. Water (50 mL) was added and the reaction mixture was
10 extracted into ethyl acetate (3 x 50 mL). The organic phase was washed sequentially with saturated NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 ethyl acetate:hexane) to give the title compound as a colorless oil (819 mg, 85%). ¹H-NMR (300 MHz, CDCl₃): δ 1.45 (s, 9H), 1.52 (m, 4H), 1.69 (m, 2H), 2.24 (s, 3H), 3.13 (t, 2H), 3.82 (t, 2H), 4.57 (bs, 1H), 6.45 (s, 1H), 6.52 (d, 1H), 6.58 (s, 1H), 7.38 (t, 1H), 7.62 (m, 2H), 7.96 (dd, 1H).

b) **2-Chlorobenzenesulfonic acid 3-[[5-(aminoiminomethyl)amino]pentoxy]-5-methylphenyl ester hydrochloride:** 2-Chlorobenzenesulfonic acid 3-[[5-(N-tert-butoxycarbonyl)amino]pentoxy]-5-methylphenyl ester (484 mg, 1.0 mmol), as prepared in the preceding step, was
20 treated with 1.0 mL of 4 N HCl in 1,4-dioxane and stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue concentrated from methylene chloride several times to give the amine salt. The salt was dissolved in DMF (10 mL) and treated with triethylamine (0.5 mL) and 1H-pyrazole-1-carboxamide hydrochloride (220 mg, 1.5 mmol). The reaction mixture was
25 stirred at room temperature for 2 days. The DMF was removed *in vacuo*. The residue was dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (3 x 50 mL), dried over K₂CO₃, and concentrated *in vacuo*. The residue was acidified with 4N HCl in 1,4-dioxane (0.5 mL) and purified by flash column

chromatography (10% methanol in methylene chloride) to give the title compound as a colorless foam (325 mg, 70%). ¹H-NMR (300 MHz, CDCl₃): δ 1.52 (m, 2H), 1.67 (m, 2H), 2.07 (m, 2H), 2.19 (s, 3H), 3.21 (t, 2H), 3.79 (t, 2H), 6.45 (s, 1H), 6.47 (s, 1H), 6.56 (s, 1H), 7.37 (t, 1H), 7.60 (m, 2H), 7.94 (d, 1H).
5 Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₁₉H₂₄N₃O₄SCl: 426.1 (M+ H). Found: 426.1

Example 42

a) 2,3-Dichlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester: A mixture of orcinol monohydrate (0.71 g, 5.0 mmol) and 2,3-dichlorobenzenesulfonyl chloride (1.23 g, 5.0 mmol) in saturated NaHCO₃ (20 mL) and ethyl ether (20 mL) was stirred vigorously at room temperature for 2 days. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic extract was washed with brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (methylene chloride to 2% ethyl acetate in methanol) to give the title compound as a pale-yellow liquid (0.89 g, 55%). ¹H-NMR (300 MHz, CDCl₃): δ 2.24 (s, 3H), 5.23 (s, 1H), 6.43 (t, 1H), 6.54 (dd, 2H), 7.34 (t, 1H), 7.75 (dd, 1H), 7.91 (dd, 1H).
10
15

b) 2,3-Dichlorobenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester: A solution of 2,3-dichlorobenzenesulfonic acid 3-hydroxy-5-methylphenol (644 mg, 2.0 mmol), as prepared in the preceding step, N-(tert-butoxycarbonyl)-4-piperidinemethanol (430 mg, 2.0 mmol), as prepared in step f of Example 1, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at 0°C was treated with diethyl azodicarboxylate (349 mg, 2.0 mmol). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction mixture was diluted with water (50 mL), and extracted into ethyl acetate (3 x 50 mL). The organic extract was washed sequentially with saturated NaHCO₃ (2 x 50 mL)
20
25

and brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:3 ethyl acetate:hexane) to give the title compound as a colorless syrup (930 mg, 88%). ¹H-NMR (300 MHz, CDCl₃): δ 1.26 (m, 2H), 1.47 (s, 9H), 1.75 (m, 2H), 1.90 (m, 1H), 2.25 (s, 3H), 2.73 (t, 2H), 3.68 (d, 2H), 4.13 (m, 2H), 6.47 (d, 1H), 6.53 (d, 1H), 6.59 (s, 1H), 7.34 (t, 1H), 7.75 (dd, 1H), 7.92 (dd, 1H).

c) **2,3-Dichlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride:** 2,3-Dichlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (530 mg, 1.0 mmol), as prepared in the preceding step, was treated with 10 mL of 4 N HCl (in 1,4-dioxane) and stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and concentrated from methylene chloride several times to give the amine salt. The salt was dissolved in DMF (10 mL) and treated with triethylamine (0.5 mL) and 1*H*-pyrazole-1-carboxamide hydrochloride (293 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 2 days. The DMF was removed *in vacuo*. The residue was dissolved in methylene chloride (200 mL), washed with 10% K₂CO₃ (3 x 50 mL), dried over K₂CO₃, and concentrated *in vacuo*. The residue was acidified with 4 N HCl in 1,4-dioxane (0.5 mL) and purified by flash column chromatography (10% methanol in methylene chloride) to give the title compound as a colorless foam (245 mg, 48%). ¹H-NMR (300 MHz, CDCl₃): δ 1.43 (m, 2H), 1.92 (m, 2H), 2.01 (m, 1H), 2.22 (s, 3H), 3.08 (t, 2H), 3.71 (d, 2H), 4.10 (m, 2H), 6.49 (s, 2H), 6.58 (s, 1H), 7.30 (bs, 4H), 7.36 (t, 1H), 7.77 (d, 1H), 7.91 (d, 1H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₀H₂₃N₃O₄SCl₂: 472.1 (M+ H) Found: 472.0.

Example 43

a) **2-Chlorobenzenesulfonic acid 3-hydroxynaphthalen-1-yl ester:**

To a solution of 1.0 g (6.24 mmol) of 1,3-dihydroxynaphthalene in methylene

-96-

chloride (20 mL) containing 1.4 mL (12.8 mmol) of N-methylmorpholine was added 1.35 g (6.40 mmol) of 2-chlorobenzenesulfonyl chloride. The reaction mixture was stirred overnight at ambient temperature, quenched with 1 N HCl, and extracted into ether. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. The product was purified by flash chromatography (methylene chloride:ether (100:0 to 95:5)) to give impure title compound (205 mg, 9.8% yield; contamination with 3-isomer). ¹H-NMR (300 MHz, DMSO-d₆) δ 8.03 (d, 1 H, J = 7 Hz), 7.2-7.7 (m, 7 H), 7.07 (d, 1 H), 6.89 (d, 1 H), 5.38 (bs, 1 H). A difference nOe experiment (irradiation at phenolic H) determined the regioisomeric composition of the major product in which enhancements of the proton doublets at 6.89 at 7.07 ppm were observed. Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for C₁₆H₁₁ClO₄S: 335.0 (M + H) and 357.0 (M + Na). Found: 334.4, 356.8.

b) 2-Chlorobenzenesulfonic acid 3-[[1-N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]naphthalen-1-yl ester: To 205 mg (0.613 mmol) of the mixture of 2-chlorobenzenesulfonic acid 3-hydroxynaphthalen-1-yl ester, contaminated with 2-chlorobenzenesulfonic acid 1-hydroxynaphthalen-3-yl ester, as prepared in the preceding step, in methylene chloride (3 mL) containing 209 mg (0.80 mmol) of triphenylphosphine, 140 mg (1.46 mmol) of N-*tert*-butoxycarbonyl-4-piperidinemethanol, as prepared in step f of Example 1, and 400 μL (3.6 mmol) of N-methylmorpholine was added 225 μL (0.796 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at ambient temperature for 30 min, quenched with H₂O, and extracted into ether. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. Partial purification was accomplished by flash chromatography (13% ether/methylene chloride) to give 173 mg (53% yield) of the title compound as a colorless hardened oil, contaminated with ca. 20% of the 1,3-regioisomer. ¹H-NMR (300 MHz, CDCl₃): δ 8.00-8.05 (m, 2 H), 7.30-7.70 (m, 6 H), 7.03 (d, 1 H), 6.91 (s, 1 H), 4.18 (bs, 2 H), 3.85 (d, 2 H), 2.76 (t, 2 H), 1.8-2.0 (m, 2 H), 1.81 (d, 2 H), 1.48 (s, 9 H).

c) **2-Chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]naphthalen-1-yl ester hydrochloride:** A solution of 153.7 mg (0.289 mmol) of 2-chlorobenzenesulfonic acid 3-[[1-N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]naphthalen-1-yl ester, as prepared in the preceding step, in methylene chloride (2 mL) was treated with 500 μ L of 4 N HCl in dioxane. The reaction mixture was stirred at ambient temperature for 1 h. Concentration *in vacuo* and repeated concentrations from methylene chloride/ether/hexane gave 143 mg of crude title compound (contaminated with ca. 20% 1,3-regioisomer) which was used as is in the next reaction. ¹H-NMR (300 MHz, CDCl₃): δ 9.75 (bs, 1 H), 9.46 (bs, 1 H), 8.02-8.05 (m, 2 H), 7.3-7.7 (m, 6 H), 7.02 (d, 1H, J = 2 Hz), 6.93 (d, 1H, J = 2 Hz), 3.91 (d, 2 H), 3.60 (d, 1 H), 2.96 (bs, 2 H), 2.03-2.17 (m, 3 H), 1.80-1.88 (m, 2 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for C₂₂H₂₂ClNO₄S: 432.1 (M+H). Found: 432.0.

d) **2-Chlorobenzenesulfonic acid 3-[[1-aminoiminomethyl)piperidin-4-yl]methoxy]naphthalen-1-yl ester hydrochloride:** A solution of 124.6 mg (0.266 mmol) of 2-chlorobenzenesulfonic acid 3-[[piperidin-4-yl]methoxy]naphthalen-1-yl ester hydrochloride, as prepared in the preceding step, in 2 mL of DMF was treated with 260 μ L (2.34 mmol) of N,N-diisopropylethylamine, and 60 mg (0.40 mmol) of 1H-pyrazole-1-carboxamide hydrochloride was stirred at ambient temperature for 2 days. The reaction mixture was concentrated to remove DMF. The residue was then treated with 25 mL of methylene chloride and 3 mL of 1 N NaOH. The organic phase was separated, dried (K₂CO₃), and concentrated. The residue was dissolved in 1 mL of methylene chloride and treated with 200 μ L of acetic acid. Preparative thin layer chromatography (two x 1000 micron silica gel plates, 20 x 20 cm) using methylene chloride:methanol:acetic acid (93.6:6.5:0.5) gave 45 mg of the title compound as a white powder after concentration from methylene chloride/ether/methylene chloride/hexane. ¹H-NMR (300 MHz, CDCl₃): δ 8.01 (dd, 1 H, J = 2, 8 Hz), 7.82-7.94 (m, 4 H), 7.51-7.63 (m, 2 H), 7.39-7.44 (m, 2 H), 6.75 (d, 1 H), 3.93 (d, 2 H, J = 6 Hz), 3.86 (d, 2 H, J = 12 Hz),

-98-

2.96 (t, 2 H, $J = 12$ Hz), 1.9-2.1 (bs, 2 H), 1.19-1.30 (m, 2 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{23}H_{24}ClN_3O_4S$: 474.1 (M+H). Found: 474.5.

Example 44

5 *a) 2-Chlorobenzenesulfonic acid 3-[[1-N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-hydroxymethylphenyl ester:* A solution of 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl) piperidin-4-yl]methoxy]-5-carbomethoxyphenyl ester (1.34 g, 2.49 mmol), as prepared in
10 borohydride (1.52 mL of 2M in tetrahydrofuran, 3.0 mmol) and then warmed to 50°C. After 3.5 h, an additional 0.5 mL of 2M lithium borohydride was added and warming was continued for a total of 10 h. The reaction was quenched with methanol and evaporated to dryness. The residue was treated with diethyl ether and methylene chloride/acetonitrile. The filtrate was evaporated to an oil, which
15 was purified by silica gel chromatography with 30% ethyl acetate in hexanes to give 0.78 g (61% yield). Mass spectrum (MALDI-TOF) calcd. for $C_{24}H_{30}N_4O_7SCl$: 412.2 (M-*tert*-butoxycarbonyl + H). Found: 412. 1.

b) 2-Chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-hydroxymethylphenylester: The
20 N-*tert*-butoxycarbonyl group of the compound of the preceding step (0.78 g, 1.53 mmol) was removed by treatment with 25% trifluoroacetic acid (12 mL) in methylene chloride at ambient temperature for 15 min. The reaction mixture was evaporated to dryness, then treated with acetonitrile and evaporated to dryness (3 times). 1H -NMR ($CDCl_3$; 300 MHz): δ 1.61-1.78 (m, 2H), 2.09 (m, 3 H), 2.49
25 (s, 2 H), 2.93 (m, 2 H), 3.46-3.53 (m, 2 H), 3.78 (d, 2 H), 4.60 (s, 1 H), 6.59-6.81 (m, 3H), 7.36-7.43 (m, 1 H), 7.57-7.66 (m, 2 H), 7.96 (m, 1 H), 8.89 (m, 1 H), 9.45 (m, 1 H). This material was dissolved in methanol (15 mL) and treated with triethylamine (0.64 mL, 4.59 mmol) and 1*H*-pyrazole-1-carboxamidine

hydrochloride (0.45 g, 3.06 mmol) and allowed to stir at ambient temperature over 4.5 days. The methanol was evaporated and the residue was placed under high vacuum. The residue was dissolved in acetonitrile and diluted with diethyl ether. The precipitate was filtered off and the filtrate was evaporated to dryness.

5 The residue was dissolved in methanol and diluted with water to produce a flocculent precipitate which was recrystallized from methanol/water. The white solid was collected by filtration and dried under high vacuum to give 210 mg. ¹H-NMR (DMSO-d₆; 300 MHz): δ 1.24 (m, 2 H), 1.77 (d, 2 H), 2.0 (m, 1 H), 3.01 (t, 2 H), 3.78 (d, 2 H), 3.87 (d, 2 H), 4.39 (s, 2 H), 6.50 (t, 1 H), 6.64 (s, 1 H), 6.84 (s, 1 H), 7.42 (m, 4 H), 7.58 (dt, 1 H), 7.8-7.96 (m, 3 H). Mass spectrum (MALDI-TOF): calcd. for C₂₀H₂₄N₃O₅SCl: 454.1 (M+ H). Found: 454.0.

Example 45

a) 3-Trifluoromethyl-5-nitrophenol:

3-Methoxy-5-

15 nitrobenzotrifluoride (5 g, 23 mmol) was dissolved in anhydrous methylene chloride (100 mL) and cooled to -80°C under a nitrogen atmosphere. To this solution was added via dropping funnel a 1 M solution of BBr₃ in methylene chloride (67.8 mL, 69 mmol). This solution was allowed to warm to room temperature and stirred for 3 days. Water was slowly added to the mixture and mixed well to quench the excess BBr₃. To this mixture ether (500 mL) was added. The organic layer was separated and extracted with 2 N NaOH (240 mL). 20 The alkaline extract was neutralized with dilute HCl and extracted with ether (3 x 300 mL). The ether extracts were combined, washed with saturated NaCl and dried over anhydrous MgSO₄. Evaporation of ether gave a brownish yellow oil which was chromatographed on a silica column to give 1.6 g (34%) of a yellow solid. ¹H-NMR (CDCl₃/CD₃OD; 300 MHz): δ 7.38-7.40 (m, 1 H), 7.82 (t, J = 2.2 Hz, 1 H), 7.95-7.96 (m, 1 H).

25 b) 3-[[1-(tert-Butoxycarbonyl)piperidin-4-yl]methoxy]-5-nitrobenzotrifluoride: The title compound was synthesized by treating 3-

-100-

(trifluoromethyl)-5-nitrophenol (1.47 g, 7.1 mmol), as prepared in the preceding step, in a manner analogous to step b of Example 19 to give 2.17 g (76 %) as an oil. ¹H-NMR (CDCl₃, 300 MHz): δ 1.24-1.38 (m, 2 H), 1.48 (s, 9H), 1.82-1.87 (m, 2 H), 1.96-2.10 (m, 1 H), 2.73-2.81 (m, 2 H), 3.93 (d, J = 6.3 Hz, 2 H), 4.09-4.21 (m, 2 H), 7.45-7.46 (m, 1 H), 7.89 (t, J = 2.2 Hz, 1H), 8.07-8.08 (m, 1H).

c) **2-Chloro-N-{3-[[1-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl}benzenesulfonamide:** To a methanolic solution of 3-[(piperidin-4-yl)methoxy]-5-nitrobenzotrifluoride (2.17 g in 200 mL), as prepared in the preceding step, and 10% Pd/C (300 mg) was stirred under a hydrogen atmosphere for 20 h. The catalyst was removed by filtration and the methanol was evaporated to give a white foam. The foam was dried under high vacuum overnight and dissolved in anhydrous methylene chloride (10 mL). The methylene chloride solution was cooled in an ice bath under a nitrogen atmosphere. To this solution, 2-chlorobenzenesulfonyl chloride (1.17 g, 5.5 mmol) and N-methylmorpholine (6.05 mmol) were added and the mixture allowed to warm to room temperature. The mixture was stirred for 2 days at which time N-methylmorpholine (200 μL) was added. The mixture heated to reflux for 3 h. The methylene chloride solution was diluted with another 50 mL of methylene chloride and extracted with 10% citric acid and saturated NaHCO₃. The organic layer was separated, washed with saturated NaCl and dried over anhydrous MgSO₄. Evaporation of the methylene chloride gave an oil which was chromatographed on a silica column to give 2.4 g (80 %) of a white solid. ¹H-NMR (CDCl₃, 300 MHz): δ 1.17-1.31 (m, 2H), 1.47 (s, 9 H), 1.75-1.80 (m, 2 H), 1.83-1.98 (m, 1 H), 2.69-2.78 (m, 2 H), 3.74 (d, J = 6.2 Hz, 2 H), 4.09-4.16 (m, 2 H), 6.81 (broad s, 1 H), 6.87-6.89 (m, 1 H), 6.90 (broad s, 1 H), 7.34-7.43 (m, 2 H), 7.50-7.54 (m, 2 H), 8.05-8.08 (m, 1H).

d) **2-{(2-Chlorobenzenesulfonyl)-[3-[[1-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid benzyl ester:** A solution of 2-chloro-N-{3-[(piperidin-4-yl)methoxy]-5-[trifluoromethyl]phenyl}benzenesulfonamide

(300 mg, 0.55 mmol), as prepared in the preceding step, in DMF (5 mL) was treated with Cs_2CO_3 (178 mg) and α -bromoacetic acid benzyl ester (138 mg). This solution was stirred overnight at room temperature. The DMF was removed under high vacuum and the resulting residue was dissolved in ethyl acetate and extracted with 10% citric acid and saturated NaCl. The ethyl acetate solution was dried over anhydrous MgSO_4 and evaporated to give an oil. This oil was chromatographed on a silica column to give 313 mg (82 %) of an oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.15-1.40 (m, 2 H), 1.48 (s, 9 H), 1.68-1.78 (m, 2 H), 1.83-1.93 (m, 1 H), 2.69-2.77 (m, 2 H), 3.68 (d, $J = 6.2$ Hz, 2 H), 4.09-4.16 (m, 2 H), 4.71 (s, 2 H), 5.17 (s, 2 H), 6.92 (broad s, 1 H), 6.98 (broad s, 1 H), 7.12-7.25 (m, 1 H), 7.28-7.39 (m, 6 H), 7.45-7.55 (m, 2 H), 7.86-7.89 (m, 1 H).

e) 2-{(2-chlorobenzenesulfonyl)-[3-[[1-[bis-(tert-butoxycarbonyl)aminoiminomethyl]piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid benzyl ester: 2-{(2-Chlorobenzenesulfonyl)-[3-[[1-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid benzyl ester (293 mg, 0.42 mmol), as prepared in the preceding step, was dissolved in 4 N HCl/dioxane and stirred for 3 h. Dioxane and excess HCl were removed under vacuum. The residue was evaporated from ether (3 x) and dried under high vacuum. The resulting HCl salt was dissolved in anhydrous tetrahydrofuran and treated with *bis*-(tert-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (130 mg, 0.42 mmol) and *N,N*-diisopropylethylamine (80.5 μL , 0.46 mmol). This mixture was stirred at room temperature for 2 days. The solvent was evaporated and the residue was chromatographed on a silica column to give 193 mg (55%) of product as a white solid. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.29-1.45 (m, 2 H), 1.50 (s, 18 H), 1.76-1.87 (m, 2 H), 1.88-2.05 (m, 1 H), 2.96-3.04 (m, 2 H), 3.69 (d, $J = 6.3$ Hz, 2 H), 4.09-4.25 (m, 2 H), 4.72 (s, 2 H), 5.17 (s, 2 H), 6.94 (broad s, 1 H), 6.98 (broad s, 1 H), 7.11-7.12 (m, 1 H), 7.28-7.40 (m, 6 H), 7.45-7.55 (m, 2 H), 7.87-7.90 (m, 1 H).

f) 2-{(2-Chlorobenzenesulfonyl)-[3-[[1-(bis-(tert-butoxycarbonyl)aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid: 2-{(2-Chlorobenzenesulfonyl)-[3-[[1-(bis-(tert-butoxycarbonyl)aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl] amino}acetic acid benzyl ester (8 mg), as prepared in the preceding step, was dissolved in methanol (2 mL). To this solution, LiOH (2 eq in H₂O 2 mL) was added and the mixture stirred over night at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned between 10% citric acid and ethyl acetate. The ethyl acetate layer was separated and washed with saturated NaCl and dried over anhydrous MgSO₄. Evaporation of the solvent gave an oil which was purified by preparative TLC to give 4.5 mg (64%) of the title compound. ¹H-NMR (CDCl₃, 300 MHz): δ 1.15-1.37 (m, 2 H), 1.47 (s, 18 H), 1.64-1.68 (m, 2 H), 1.76-1.78 (m, 1 H), 2.81-2.88 (m, 2 H), 3.60 (d, J = 6.2 Hz, 2 H), 3.80-4.25 (m, 2 H), 4.40 (s, 2 H), 6.71 (broad s, 1 H), 7.04 (broad s, 1 H), 7.05 (broad s, 1 H), 7.18-7.20 (m, 1 H), 7.38 (s, 1 H), 7.39 (s, 1 H), 7.80 (d, J = 7.8 Hz, 1 H), 10.09 (broad s, 1H).

g) 2-{(2-Chlorobenzenesulfonyl)-[3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid hydrochloride: The title compound was synthesized by treating 2-{(2-chlorobenzenesulfonyl)-[3[[1-(bis-(tert-butoxycarbonyl)aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid, as prepared in the preceding step, with 4 N HCl in dioxane for 5 h. Removal of solvent and evaporation from ether (3 x) gave 3.3 mg (100%) of the title compound. ¹H-NMR (CD₃OD, 300 MHz): δ 1.25-1.45 (m, 2 H), 1.91-1.95 (m, 2 H), 2.10-2.61 (m, 1 H), 3.08-3.18 (m, 2 H), 3.72-3.91 (m, 4 H), 4.69 (s, 2 H), 7.08 (s, 1 H), 7.11 (s, 1 H), 7.20 (s, 1 H), 7.37-7.42 (m, 1 H), 7.56-7.66 (m, 2 H), 7.87-7.90 (m, 1 H). Mass spectrum (MALDI-TOF) calcd. for C₂₂H₂₄ClF₃N₄O₅S: 549.1 (M+H). Found: 548.7.

The following additional compound was synthesized using a process analogous to steps (a)-(e) and (g) in Example 45:

Example 46

5 *6-((2-Chlorobenzenesulfonyl)-{3-[[1-aminoiminomethyl]piperidin-4-yl]methoxy]-5-methylphenyl}amino)hexanoic acid methyl ester hydrochloride:*

¹H-NMR (300 MHz, DMSO-d₆) δ 1.22-1.49 (m, 8 H), 1.77 (d, J = 11.9 Hz, 2 H), 1.98 (m, 1 H), 2.19 (s, 3 H), 2.25 (t, J = 7.2 Hz, 2 H), 3.01 (t, J = 12.2 Hz, 2 H), 3.57 (s, 3 H), 3.73 (m, 4 H), 3.89 (d, J = 13.5 Hz, 2 H), 6.50 (s, 1 H), 6.59 (s, 1 H), 6.70 (s, 1 H), 7.46 (m, 1 H), 7.51 (br s, 3 H), 7.69 (m, 2 H), 7.79 (d, J = 7.9 Hz, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₇H₃₇ClN₄O₅S: 565.2 (M + H); Found: 565.7.

The following additional compound was synthesized using a process analogous to step (f) in Example 45:

Example 47

15 *6-((2-Chlorobenzenesulfonyl)-{3-[[1-aminoiminomethyl]piperidin-4-yl]methoxy]-5-methylphenyl}amino)hexanoic acid hydrochloride:* ¹H-NMR (300 MHz, DMSO-d₆) δ 1.22-1.46 (m, 8 H), 1.77 (d, J = 11.1 Hz, 2 H), 1.98 (m, 1 H), 2.15 (t, J = 7.3 Hz, 2 H), 2.19 (s, 3 H), 3.01 (t, J = 12.0 Hz, 2 H), 3.73 (m, 4 H), 3.88 (d, J = 13.2 Hz, 2 H), 6.51 (s, 1 H), 6.59 (s, 1 H), 6.70 (s, 1 H), 7.42 (br s, 3 H), 7.48 (m, 1 H), 7.69 (m, 2 H), 7.80 (d, J = 7.8 Hz, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for C₂₆H₃₅ClN₄O₅S: 551.2 (M + H), 573.2 (M + Na); Found: 551.6, 573.3.

The following additional compound was synthesized using a process analogous to steps (a)-(g) in Example 45:

Example 48

5 *6-((2-Chlorobenzenesulfonyl)-{3-[(1-aminoiminomethyl)piperidin-4-yl]methoxy}-5-(trifluoromethyl)phenyl)amino)hexanoic acid:* ¹H-NMR (300 MHz, CDCl₃/TFA) δ 1.26-1.68 (m, 8 H), 1.98-2.20 (m, 3 H), 2.40 (t, 2 H), 3.16 (t, 2 H), 3.79-3.86 (m, 6 H), 6.90 (s, 1 H), 7.05 (d, 2 H), 7.32 (t, 1 H), 7.49-7.57 (m, 2 H), and 7.83 (dd, 1 H). Mass spectrum (MALDI-TOF, (α -cyano-4-hydroxycinnamic acid matrix) calcd. for C₂₆H₃₂N₄O₅SF₃Cl: 605.2 (M + H).
10 Found: 605.1.

The following additional compound was synthesized using a process analogous to steps (a)-(e) and (g) in Example 45:

Example 49

15 *N-(2-Propyl)-N-{{3-(1-aminoiminomethyl)piperidin-4-ylmethoxy}-5-trifluoromethyl}phenyl-2-chlorobenzenesulfonamide hydrochloride:* ¹H-NMR (300 MHz, DMSO-d₆) δ 1.09 (d, J = 6.7 Hz, 6 H), 1.14-1.37 (m, 2 H), 1.75 (d, J = 11.17 Hz, 2 H), 1.95-1.99 (m, 1 H), 2.92 (t, J = 12.2 Hz, 2 H), 3.87-3.90 (m, 4 H), 4.54-4.63 (m, 1 H), 6.78 (s, 1 H), 6.85 (s, 1 H), 7.33 (s, 1 H), 7.44-7.50 (m, 1 H), 7.66-7.82 (m, 3 H): Mass spectrum (MALDI-TOF, sinapinic acid matrix)
20 calcd. for C₃₃H₂₈N₄O₃ClSF₃, 533.2 (M + H): Found: 533.3.

Example 50

a) **2-[N-1,3-[[1-[bis-(tert-butoxycarbonyl)aminoiminomethyl]piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]benzenesulfonamide}acetic acid:**

2-{(2-Chlorobenzenesulfonyl)-[3-[[1-[bis-(tert-butoxycarbonyl)aminoiminomethyl]piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid benzyl ester (173 mg), as prepared in step e of Example 27, in MeOH containing 10% Pd/C was stirred under a hydrogen atmosphere for 1.5 h. The catalyst was removed by filtration and the solvent evaporated to give 147 mg of the product as a white solid. ¹H-NMR (CDCl₃, 300 MHz): δ 1.51 (s, 18 H), 1.63-1.77 (m, 2 H), 1.91-1.95 (m, 2 H), 2.09-2.18 (m, 1 H), 3.35-3.52 (m, 2 H), 3.82 (d, J = 6.1 Hz, 2 H), 4.07-4.11 (m, 2 H), 4.39 (s, 2 H), 6.81 (broad s, 1 H), 6.84 (broad s, 1 H), 6.97 (broad s, 1 H), 7.29-7.69 (m, 5 H).

b) **2-{Benzenesulfonyl-[3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid hydrochloride:**

2-{Benzenesulfonyl-[3-[[1-[(bis-tert-butoxycarbonyl)aminoiminomethyl]piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino}acetic acid, as prepared in the preceding step, was treated with 4 N HCl in dioxane for 5 h. The reaction mixture was concentrated in vacuo and the final product was crystallized from MeOH/Et₂O to give 50 mg (60%). ¹H-NMR (CD₃OD, 300 MHz): δ 1.43-1.51 (m, 2 H), 1.93-1.97 (m, 2 H), 2.14-2.15 (m, 1H), 3.09-3.17 (m, 2 H), 3.86-3.97 (m, 4 H), 4.46 (s, 2 H), 6.95 (broad s, 1 H), 7.11 (s, 1 H), 7.12 (s, 1 H), 7.53-7.69 (m, 5 H). Mass spectrum (MALDI-TOF) calcd. for C₂₂H₂₃F₃N₄O₅S: 515.2 (M+H). Found: 515.0.

Example 51

a) **2-Chloro-N-1,3-[[1-[bis-(tert-butoxycarbonyl)aminoiminomethyl]piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]benzenesulfonamide:** 2-Chloro-N-{3-[[1-(tert-butoxycarbonyl)piperidin-4-

yl]methoxy]-5-[trifluoromethyl]phenyl}benzenesulfonamide, prepared as in step c of Example 27, was treated in manner similar to step e of Example 27, except DMF was used instead of tetrahydrofuran as solvent, to give 100 mg (10%) of product as a white solid. ¹H-NMR (CDCl₃, 300 MHz): δ 1.26-1.28 (m, 2 H), 1.49 (s, 18 H), 1.72-1.88 (m, 2 H), 2.01-2.04 (m, 1 H), 2.93-3.04 (m, 2 H), 3.76 (d, J = 6.3 Hz, 2 H), 4.09-4.22 (m, 2 H), 6.80 (broad s, 1 H), 6.87-6.88 (m, 1 H), 6.93 (broad s, 1 H), 7.36-7.48 (m, 1 H), 7.50-7.53 (m, 2 H), 8.06-8.09 (m, 1 H).

b) 2-Chloro-N-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl}benzenesulfonamide hydrochloride: 2-Chloro-N-{3-[[1-[(bis-*tert*-butoxycarbonyl)aminoiminomethyl]piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl}benzenesulfonamide, as prepared in the preceding step, was treated with 4 N dioxane in HCl and stirred for 5 h. Dioxane and excess HCl were removed under vacuum and the resulting residue was evaporated from Et₂O (3 x). The resulting residue was dried under high vacuum to give a white solid 35 mg (100%). ¹H-NMR (CD₃OD, 300 MHz): δ 1.25-1.28 (m, 2 H), 1.90-1.95 (m, 2 H), 2.03-2.11 (m, 1 H), 3.08-3.30 (m, 2 H), 3.84 (d, J = 6.1 Hz, 2 H), 3.91-3.96 (m, 2 H), 6.82 (s, 1 H), 6.92 (s, 1 H), 6.97 (s, 1 H), 7.44-7.49 (m, 1 H), 7.56 (s, 1 H), 7.57 (s, 1 H), 8.11 (d, J = 7.4 Hz, 1 H). Mass spectrum (MALDI-TOF) calcd. for C₂₀H₂ClF₃N₄O₃S: 491.1 (M+H). Found: 490.9.

Example 52

a) N-(3-Nitrophenyl)-2-chlorobenzenesulfonamide: To 1.79 g (13.0 mmol) of 3-nitroaniline and 1.68 mL (15.3 mmol) of 4-methylmorpholine in 25 mL of anhydrous dichloromethane was added 2.50 g (11.8 mmol) of 2-chlorobenzenesulfonyl chloride. After stirring for 14 h. the mixture washed with 2 N HCl (3 x 20 mL) and extracted with 1 N NaOH (2 x 20 mL). The organic layer was washed with brine (25 mL), dried (Na₂SO₄) and concentrated to afford 0.62 g (22%) of the disulfonated byproduct, N-(3-nitrophenyl)-2,2'-dichlorobenzenesulfonamide. The combined NaOH extracts were acidified with

2 N HCl and extracted with ethyl acetate HCl (3 x 20 mL). The combined ethyl acetate extracts were then washed with brine (25 mL), dried (Na_2SO_4) and concentrated to give 2.68 g (73%) of the title compound as a cream-colored solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.09 (m, 1 H), 7.92-7.98 (m, 2 H), 7.37-7.55 (m, 6 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $\text{C}_{12}\text{H}_9\text{ClN}_2\text{O}_4\text{S}$: 335.0 (M + Na), 337.0 (M + Na) (^{37}Cl). Found: 334.9, 336.9.

b) *N-Benzyl-N-(3-nitrophenyl)-2-chlorobenzenesulfonamide*: To 1.40 g (4.48 mmol) of N-(3-nitrophenyl)-2-chlorobenzenesulfonamide in 3.0 mL of anhydrous N,N-dimethylformamide under nitrogen was added 0.929 g (6.72 mmol) of powdered anhydrous potassium carbonate and 0.586 mL (4.93 mmol) of benzyl bromide. After stirring for 1 h, the mixture was partitioned between 20 mL of ethyl acetate and 100 mL of water. The aqueous layer was extracted with 10 mL of ethyl acetate and the combined organic phases washed with water (2 x 50 mL), brine (50 mL) and dried (Na_2SO_4). Concentration afforded 1.90 g of a residue which was heated under vacuum (0.1 torr/70°C/3 h) to yield 1.78 g (99%) of title compound as a light yellow resin. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.91-8.02 (m, 2 H), 7.48-7.59 (m, 2 H), 7.22-7.39 (m, 4 H), 5.09 (s, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $\text{C}_{19}\text{H}_{15}\text{ClN}_2\text{O}_4\text{S}$: 425.0 (M + Na), 427.0 (M + Na) (^{37}Cl). Found: 425.0, 427.0.

c) *N-Benzyl-N-(3-aminophenyl)-2-chlorobenzene-sulfonamide*: To 0.795 g (1.97 mmol) of N-benzyl-N-(3-nitrophenyl)-2-chlorobenzenesulfonamide in 10 mL of tetrahydrofuran was added 60 mg of 10% palladium on carbon. After stirring the mixture under a balloon of hydrogen for 18 h, the mixture was filtered (Diatomaceous earth) and concentrated to afford a yellow syrup. Heating the residue under vacuum (50-60°C/2.5 h) afforded 0.727 g (99%) of the title compound as a yellow resin which crystallized on standing. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.88 (dd, 1 H, J=7.9, 1.6 Hz), 7.53 (dd, 1 H, J=8.0, 1.3 Hz), 7.40 (td, 1 H, J=7.9, 1.6 Hz), 7.20-7.30 (m, 6 H), 6.90 (t, 1 H, J=8.3 Hz), 6.46 (m, 3 H), 5.02 (s, 2 H), 3.35 (br, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_2\text{S}$: 373.1 (M + H), 395.1 (M + Na). Found: 373.0, 395.1.

d) *N-Benzyl-N-[[3-(1-tert-butoxycarbonylpiperidin-4-yl)carbonylamino]phenyl]-2-chlorobenzenesulfonamide*: To 479 mg (2.09 mmol) of 1-tert-butoxycarbonylisonipecotic acid, as prepared in step e of Example 1, and 924 mg (2.09 mmol) of Castro's Reagent (benzotriazolyloxytris(dimethylaminophosphonium hexafluorophosphate, BOP) in 3.0 mL of anhydrous N,N-dimethylformamide (DMF) was added 497 gL (2.85 mmol) of N,N-diisopropylethylamine and the mixture stirred under nitrogen for 10 min. A solution of 710 mg (1.90 mmol) N-benzyl-N-(3-aminophenyl)-2-chlorobenzenesulfonamide in 1.0 mL of DMF was added. After stirring for 16 h, 25 mL of saturated NaHCO₃ was added and the mixture poured into 45 mL of water. The mixture was extracted with ethyl acetate (2 x 25 mL) and the combined extracts washed with water-brine (1:1, 2 x 50 mL), brine (20 mL), dried (Na₂SO₄) and concentrated to afford 1.06 g of a brown foam. Flash chromatography on 50 g of silica eluting with 8% ethyl acetate/dichloromethane afforded 56 mg (8%) of unreacted starting aniline. Elution with 10% ethyl acetate/dichloromethane afforded 583 mg (48%) the title compound (53% based on recovered starting material) as a pale amber resin which was crystallized to a light pink solid from ether-hexane. ¹H-NMR (300 MHz, CDCl₃): δ 7.86 (dd, 1H, J=8.0, 1.6 Hz), 7.55 (m, 1H), 7.46 (td, 1 H, J=7.7, 1.6 Hz), 7.26 (m, 5 H), 7.13 (m, 3 H), 6.81 (d, 1 H, J=7.8 Hz), 5.03 (s, 2 H), 4.18 (br, 2 H), 2.75 (br t, 2 H, J=11.8 Hz), 2.30 (m, 1 H), 1.83 (br d, 2 H, J= 11.2 Hz), 1.70 (td, 2 H, J= 11.8, 4.2 Hz), 1.47 (s, 9 H),. Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₃₀H₃₄ClN₃O₃S: 606.2 (M + Na). Found: 606.1.

e) *N-Benzyl-N-[[[3-(1-tert-butoxycarbonyl)piperidin-4-ylcarbonyl]benzyloxycarbonylmethyl]amino]phenyl]-2-chlorobenzenesulfonamide*: To 200 mg (0.342 mmol) of N-benzyl-N-[[3-(1-tert-butoxycarbonylpiperidin-4-yl)carbonylamino]phenyl]-2-chlorobenzenesulfonamide in 2.0 mL of anhydrous DMF at -10°C under nitrogen was added 15.0 mg (0.616 mmol) of dry sodium hydride. After stirring for 5 min, 59.6 μL (0.376 mmol) of benzyl bromoacetate was added. After 1 h, the mixture was warmed to room temperature. After 2.5

h, an additional 59.6 μ L (0.376 mmol) of benzyl bromoacetate was added and the mixture stirred for 30 min. The reaction was quenched with 0.5 mL of 10% citric acid, poured into 60 mL of water and extracted with ethyl acetate (2 x 15 mL). The combined extracts were washed with water (2 x 50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated to 298 mg of an amber oil. Chromatography on three preparatory TLC plates (Whatman, 20 x 20 cm, 1000 μ M thickness) developed with 4% methanol-dichloromethane afforded 126 mg (50%) of the title compound as a pale yellow resin along with 66 mg (33%) of recovered starting secondary amide. Yield based on recovered starting material was 75%. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.91 (dd, 1 H, $J=8.0, 1.6$ Hz), 7.44-7.54 (m, 2 H), 7.09-7.40 (m, 15 H), 5.15 (s, 2 H), 4.96 (s, 2 H), 4.15 (s, 2 H), 3.94 (br, 2 H), 2.33 (br, 2 H), 2.15 (m, 1 H), 1.44 (s, 9 H), 1.35-1.65 (m, 4 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $\text{C}_{39}\text{H}_{42}\text{ClN}_3\text{O}_7\text{S}$: 754.2 (M + Na). Found: 754.3.

f) *N-Benzyl-N-[[[3-(1-tert-butoxycarbonyl)piperidin-4-ylmethyl]benzyloxycarbonylmethyl]amino]phenyl]-2-chlorobenzenesulfonamide*: To 0.386 mL (0.771 mmol) of 2 M lithium borohydride in tetrahydrofuran was added 1.0 mL of tetrahydrofuran followed by 0.195 mL (1.54 mmol) of chlorotrimethylsilane. After stirring for 5 min, 188 mg (0.257 mmol) of *N*-benzyl-*N*-[[[3-(1-tert-butoxycarbonyl)piperidin-4-ylcarbonyl]benzyloxycarbonylmethyl]amino]phenyl]-2-chlorobenzenesulfonamide in 2.0 mL of tetrahydrofuran was added, the mixture heated at 50°C under nitrogen for 3 h, cooled to room temperature over 1 h and let stand for 10 h. After quenching the reaction with 0.2 mL of MeOH, 1.0 mL of saturated NaHCO_3 was added, the mixture stirred for 2 min and then 2 mL of 1 M pH 7 buffer was added. The mixture was extracted with ethyl acetate (2 x 10 mL) and the combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated to 190 mg of colorless resin. Chromatography on a Waters Associates 10 g silica Sep-Pak SPE column eluting with 4% ethyl acetate-dichloromethane afforded 78.6 mg (42 %) of the title compound as a colorless

resin. ¹H-NMR (300 MHz, CDCl₃) δ 7.86 (dd, 1H, J=7.9, 1.6 Hz), 7.52 (dd, 1H, J=7.9, 1.3 Hz), 7.43 (td, 1H, J=7.7, 1.6 Hz), 7.19-7.38 (m, 11 H), 6.93 (t, 1 H, J=8.0 Hz), 6.30-6.40 (m, 3 H), 5.00 (s, 2 H), 4.71 (d, 2 H, J=3.2 Hz), 4.09 (br t, 2 H), 3.87 (s, 2 H), 3.03 (d, 2 H, J=6.8 Hz), 2.56 (br t, 2 H, J=12.2 Hz), 1.60 (m, 3 H), 1.47 (s, 9 H), 0.90-1.21 (m, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₃₉H₄₄ClN₃O₆S: 740.3 (M + Na). Found: 741.0.

g) *N-Benzyl-N-[[3-(1-aminoiminomethyl)piperidin-4-ylmethyl]benzyloxycarbonylmethyl]-amino]phenyl]-2-chlorobenzenesulfonamide*: To 70.0 mg (0.195 mmol) of N-benzyl-N-[3-(1-*tert*-butoxycarbonyl)piperidin-4-ylmethyl]benzyloxycarbonylmethyl]amino]phenyl]-2-chlorobenzenesulfonamide in 1.5 mL of anhydrous dichloromethane was added 0.50 mL of trifluoroacetic acid. After stirring for 20 min, the solution was concentrated and placed under vacuum (0.1 torr/1 h) to afford 70 mg of a colorless resin. Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₃₄H₃₆ClN₃O₄S: 618.2 (M + H). Found: 618.2. To 61 mg of this residue in 2.0 mL of anhydrous methanol was added 48.7 mg (0.332 mmol) aminoiminomethanesulfonic acid and 136 gL (0.780 mmol) of N,N-diisopropylethylamine and the mixture stirred for 1.25 h. 2 mL of saturated NaHCO₃ and 2 mL of water were added and the mixture stirred for 10 min. After concentration to dryness, the residue was partitioned between 10 mL of water and 10 mL of dichloromethane. The aqueous phase was extracted with dichloromethane (4 x 5 mL) and the combined organic phases dried (Na₂SO₄) and concentrated to afford 60.1 mg (93%) of the title compound as a colorless glass. ¹H-NMR (300 MHz, CDCl₃) δ 7.84 (dd, 1H, J=8.0, 1.6 Hz), 7.51 (dd, 1H, J=8.0, 1.3 Hz), 7.43 (td, 1H, J=7.7, 1.6 Hz), 7.20-7.38 (m, 11 H), 6.93 (t, 1H, J=8.1 Hz), 6.34 (m, 3 H), 5.10 (s, 2 H), 4.95 (s, 2 H), 3.88 (obscured br d, 2 H), 3.86 (s, 2 H), 3.02 (d, 2 H, J=6.3 Hz), 2.84 (t, 2 H, J= 12.9 Hz), 1.70 (m, 3 H), 1.13 (m, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for C₃₄H₃₆ClN₃O₄S: 660.2 (M + H). Found: 660.0.

-111-

h) *N-Benzyl-N-[[3-(1-aminoiminomethyl)piperidin-4-ylmethyl]carboxymethyl]amino]phenyl]-2-chlorobenzenesulfonamide*: To 54.2 mg (82.1 μ mol) of *N*-benzyl-*N*-[[3-(1-aminoiminomethyl)piperidin-4-ylmethyl]benzyloxycarbonylmethyl]amino]phenyl]-2-chlorobenzenesulfonamide in 2 mL of tetrahydrofuran:methanol (1:1) was added 410 μ L of 1 M aqueous lithium hydroxide. After stirring for 30 min, the mixture was concentrated to near dryness. The residue was dissolved in 8 mL of water, acidified with 1 M HCl and extracted with ethyl acetate (5 x 8 mL). The combined extracts were dried (Na_2SO_4) and concentrated to a white residue. Trituration with ether and concentration afforded 41.4 mg (83%) of the title compound as a white solid. ^1H -NMR (300 MHz, CD_3OD) δ 7.85 (dd, 1H, $J=7.9, 1.5$ Hz), 7.65 (dd, 1H, $J=8.0, 1.1$ Hz), 7.56 (td, 1H, $J=7.7, 1.5$ Hz), 7.24-7.38 (m, 6H), 6.95 (t, 1H, $J=8.1$ Hz), 6.44 (d, 2H, $J=9.6$ Hz), 6.36 (m, 2H), 3.92 (s, 2H), 3.87 (d, 2H, $J=13.8$ Hz), 3.11 (d, 2H, $J=7.0$ Hz), 2.98 (t, 2H, $J=12.1$ Hz), 1.86 (m, 1H), 1.76 (d, 2H, $J=13.3$ Hz), 1.90 (m, 2H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $\text{C}_{28}\text{H}_{32}\text{ClN}_5\text{O}_4\text{S}$: 570.2 ($M + H$). Found: 570.0.

Example 53

a) *2-Chlorobenzenesulfonic acid 3-[[1-(*N*-methoxycarbonylaminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester*: A suspension of 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (0.3 g, 0.63 mmol), as prepared in the step f of the Example 3, in acetonitrile (10 mL) was treated with diisopropyl ethylamine (0.11 mL, 0.63 mmol) followed by dimethyl pyrocarbonate (0.067 mL, 0.63 mmol) and stirred at ambient temperature for 41 h. The reaction mixture was evaporated to dryness and the residue was partitioned between methylene chloride and water. The organic layer was separated and washed with water. The aqueous layers were combined and extracted with methylene chloride. The organic layers were combined, washed

-112-

with brine, dried, and evaporated to dryness. The residue was applied to a 10 g SepPak silica-gel column and eluted with methylene chloride, followed by 10%, then 20% ethyl acetate in methylene chloride. The appropriate fractions were combined and evaporated to dryness. The residue was treated with hexane overnight. The solid was collected by filtration, washed with ether, and dried under high vacuum to give the title compound as a white solid (0.188 g, 61%).¹H-NMR (300 MHz, CDCl₃) δ 1.33 (dq, 2 H), 1.87 (br d, 2 H), 2.00 (m, 1 H), 2.24 (s, 3 H), 2.89 (dt, 2 H), 3.69 (m, 5 H), 4.25 (br d, 2 H), 6.49 (br t, 1 H), 6.52 (br s, 1 H), 6.58 (br s, 1 H), 7.39 (dt, 1 H), 7.56-7.65 (m, 2 H), and 7.97 (m, 1 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for C₂₂H₂₆N₃O₆SCl: 496.1 (M + H). Found: 495.9.

Example 54

a) *N-carboxymethyl-1H-pyrazole-1-carboxamide*: A solution of commercially available 1H-pyrazole-1-carboxamide hydrochloride (2.92 g, 0.02 mol) in anhydrous N,N-dimethylformamide (20 mL) and methylene chloride (20 mL) was treated with N,N-diisopropylethylamine (3.5 mL, 0.02 mol) followed by dimethyl pyrocarbonate (2.14 mL, 0.02 mol). The reaction mixture was stirred at ambient temperature for 3 h, then evaporated to dryness. The residue was applied to a 10 g SepPak silica-gel column and eluted with methylene chloride. The appropriate fractions were combined and evaporated. The residue was applied to another 10 g SepPak silica-gel column and eluted with methylene chloride. The appropriate fractions were combined and evaporated. The residue was dissolved in methylene chloride and washed with water. The organic layer was separated, dried, and evaporated to give the title compound as a white solid (2.83 g, 84%).¹H-NMR (300 MHz, CDCl₃) δ 3.81 (s, 3 H), 6.44 (dd, 1 H), 7.64 (br m, 1 H), 7.71 (dd, 1 H), 8.44 (dd, 1 H), and 9.04 (br m, 1 H).

b) *N,N'-bis-carboxymethyl-1H-pyrazole-1-carboxamide*: A suspension of sodium hydride (0.85 g, 0.035 mol) in anhydrous tetrahydrofuran

(30 mL) was cooled in an ice-water bath and treated with a solution of N-carboxymethyl-1*H*-pyrazole-1-carboxamidine (2.83 g, 0.017 mol), as prepared in the preceding step, in anhydrous tetrahydrofuran (15 mL) via a cannula. After stirring for 0.5 h, dimethyl pyrocarbonate (1.8 mL, 0.017 mol) was added to the reaction mixture via syringe. The reaction mixture was allowed to warm to room temperature. The reaction was quenched with water and treated with 1N HCl until pH 7.0. The mixture was extracted with ethyl acetate (three times). The aqueous layer was treated with saturated sodium chloride solution and re-extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried, and evaporated to dryness. The residue was recrystallized from hexane, collected by filtration, washed with hexane, and dried under high vacuum to give a mixture consisting of two bis-carboxymethylated materials in a ratio of (31%) A and (69%) B. ¹H-NMR (300 MHz, CDCl₃) of A: δ 3.80 (s, 6 H), 6.44 (m, 1 H), 7.71 (m, 1 H), 8.44 (dd, 1 H), and 9.04 (br m, 1 H). ¹H-NMR (300 MHz, CDCl₃) of B: δ 3.85 (s, 3 H), 3.87 (s, 3 H), 6.47 (m, 1 H), 7.66 (m, 1 H), 8.30 (dd, 1 H), and 9.29 (br m, 1 H).

c) 2-Chlorobenzenesulfonic acid 3-[[1-((N-methoxycarbonylamino)-N-methoxycarbonyliminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester: A solution of 2-chlorobenzenesulfonic acid 3-[(piperidin-4-yl)-methoxy]-5-methylphenyl ester (0.25 g, 0.5 mmol), as prepared in the step e of the Example 3, and triethylamine (0.077 mL, 0.55 mmol) in anhydrous tetrahydrofuran (10 mL) was treated with N,N'-bis-carboxymethyl-1*H*-pyrazole-1-carboxamidine (0.18 g, 0.55 mmol), as prepared in the preceding step, at ambient temperature. The reaction mixture was evaporated to dryness and the residue was partitioned between methylene chloride and water. The organic layer was separated and washed with water. The aqueous layers were combined and extracted with methylene chloride. The organic layers were combined, washed with brine, dried, and evaporated to dryness. The residue was applied to a 10 g SepPak silica-gel column and eluted with methylene chloride, followed by 10% ethyl acetate in methylene chloride. The appropriate fractions

were combined and evaporated to dryness. The residue was treated with hexane and sonicated. The resulting solid was collected by filtration, washed with ether, and dried under high vacuum to give the title compound as a white solid (0.189 g, 68%). ¹H-NMR (300 MHz, CDCl₃/TFA) δ 1.25-1.31 (m, 1 H), 1.69-1.80 (m, 2 H), 2.03-2.31 (m, 5 H), 3.48 (t, 2 H), 3.76 (d, 2 H), 3.88 (s, 6H), 4.03 (br d, 2 H), 6.50 (s, 1 H), 6.54 (s, 1 H), 6.59 (s, 1 H), 7.37 (br t, 1 H), 7.57-7.65 (m, 2 H), and 7.95 (d, 1 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for C₂₄H₂₈N₃O₈SCl: 554.3 (M + H) and 576.3 (M + Na). Found: 554.3 and 576.3.

Example 55

2-Chlorobenzenesulfonic acid 3-[[1-((N,N-di(methoxycarbonyl)amino)-N-methoxycarbonyliminomethyl)piperidin-4-yl]methoxy]-5-methylphenylester:

A suspension of 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (0.2 g, 0.45 mmol), as prepared in the step (f) of Example 3, in acetonitrile (10 mL) was treated with N,N-diisopropylethylamine (0.08 mL, 0.45 mmol) followed by excess dimethyl pyrocarbonate. The reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was evaporated to dryness. The residue was applied to a 10 g SepPak silica-gel column and eluted with 5%, then 10% ethyl acetate in methylene chloride. The appropriate fractions were combined and evaporated to dryness. The residue was recrystallized from ethanol and water. The solid was collected by filtration and dried under high vacuum to give the title compound as a white foam (0.190 g, 69%). ¹H-NMR (300 MHz, CDCl₃) δ 1.25-1.55 (m, 2 H), 1.90 (br d, 2 H), 2.04 (m, 1 H), 2.23 (s, 3 H), 3.03 (m, 2 H), 3.70-3.75 (m, 5 H), 3.85-3.94 (m, 7 H), 4.82 (br d, 1 H), 6.51 (br t, 1 H), 6.53 (br s, 1 H), 6.57 (br s, 1 H), 7.39 (m, 1 H), 7.56-7.65 (m, 2 H), and 7.97 (dd, 1 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for C₂₆H₃₀N₃O₁₀SCl: 612.4 (M + H). Found: 612.5.

Example 56

a) **2-Chlorobenzenesulfonic acid 3-formylphenyl ester:** To a solution of 2.0 (16.4 mmol) of 3-hydroxybenzaldehyde in methylene chloride (10 mL) containing 10 mL (78.5 mmol) of N,N-diisopropylethylamine was added 3.45 g (16.3 mmol) of 2-chlorobenzenesulfonyl chloride. After stirring at ambient temperature for 1 h, the reaction mixture was quenched with 3 N HCl (acidic to pH paper) and extracted into diethyl ether. The organic phase was washed with 3 N HCl and then saturated sodium bicarbonate. Drying (MgSO₄) and purification by flash chromatography (methylene chloride/petroleum ether 4:1) gave 4.28 g of the title compound as a colorless solid. ¹H-NMR (300 MHz, CDCl₃) δ 9.94 (s, 1 H), 7.96 (d, 1 H), 7.94 (d, 1 H), and 7.36 - 7.8 (m, 6 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for C₁₃H₉ClO₄S: 319.0 (M + Na). Found: 319.0.

b) **3-(tert-Butyloxycarbonyl)aminopropionaldehyde:** A mixture of 2.0 g (11.6 mmol) of 3-N-(tert-butyloxycarbonyl)propanol and 4.45 g (21 mmol) of pyridinium chlorochromate in methylene chloride (30 mL) was stirred at ambient temperature for 30 min. Another 3 g of pyridinium chlorochromate was added and the reaction mixture further stirred for 30 min. The mixture was filtered through a thick pack of silica gel (diethyl ether/methylene chloride (1:9) elution) and concentrated. The crude product (1.2 g) was used as is: ¹H-NMR (300 MHz, CDCl₃) δ 9.8 (1 H), 4.91 (bs, 1 H), 3.42 (q, 2 H), 2.71 (t, 2 H), and 1.43 (s, 9 H).

c) **2-Chlorobenzenesulfonic acid 3-N-methylaminomethylphenyl ester:** A mixture of 500 mg (1.73 mmol) of 2-chlorobenzenesulfonic acid 3-formylphenyl ester, as prepared in step a of this Example, and 800 mg (11.9 mmol) of methylamine hydrochloride in methylene chloride/methanol (10:1; 11 mL) was treated with 800 mg (3 mmol) of tetramethylammonium triacetoxyborohydride. The reaction mixture was stirred for 1 h, quenched with saturated sodium bicarbonate until foaming ceased, and extracted into diethyl

ether. The organic phase was washed with saturated sodium bicarbonate solution, (3 x 20 mL), dried (K_2CO_3), and concentrated to give 508 mg of crude product (94% yield) which was used without further purification: Mass spectrum (MALDI-TOF; α -cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{14}H_{14}ClNO_3S$: 312.1 (M + H). Found: 312.1.

d) **2-Chlorobenzenesulfonic acid 3-[[N-3-*tert*-butoxycarbonylamino)propyl]-N-methylamino]methylphenyl ester:** To a solution of 190 mg (0.610 mmol) of 2-chlorobenzenesulfonic acid 3-N-methylaminomethylphenyl ester, as prepared in the preceding step, and 168 mg (0.97 mmol) of 3-(*tert*-butoxycarbonyl)aminopropionaldehyde, as prepared in step b of this Example, in 10 mL of methylene chloride/1 mL methanol was added 400 mg (1.5 mmol) of tetramethylammonium triacetoxymethylborohydride. After stirring for 30 min, another 90 mg of the aldehyde was added. The reaction mixture was stirred for 30 min, quenched with saturated sodium bicarbonate solution and extracted into diethyl ether (70 mL). The organic extract was washed with 4 x 20 mL of sodium bicarbonate, dried ($MgSO_4$), and purified by flash chromatography (methylene chloride/diethyl ether (1:1) to methylene chloride/diethyl ether/methanol (40:50:10) to give 158 mg of the title compound as an oil: 1H -NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, 1 H), 7.54-7.64 (m, 2 H), 7.36 (dt, 1 H), 6.9-7.21 (m, 4 H), 3.41 (s, 2 H), 3.14 (q, 2 H), 2.36 (t, 2 H), and 1.47 (s, 9 H).

e) **2-Chlorobenzenesulfonic acid 3-[(N-3-aminopropyl)-N-methylamino]methylphenyl ester dihydrochloride:** A solution of 156 mg of 2-chlorobenzenesulfonic acid 3-[[N-3-*tert*-butoxycarbonylamino)propyl]-N-methylamino]methylphenyl ester, as prepared in the preceding step, in methylene chloride (1 mL) was treated with 1 mL of 4 N HCl in dioxane. The reaction mixture was stirred for 30 min, and concentrated from diethyl ether/hexane to give 160 mg of the title compound as a solid: (MALDI-TOF; gentisic acid matrix) calcd. for $C_{17}H_{21}ClN_2O_3S$: 369.1 (M + H). Found: 369.0.

f) 2-Chlorobenzenesulfonic acid 3-{N-[[3-(aminoiminomethyl)amino]propyl]-N-(methyl)aminomethyl}phenylester acetic acid salt:

A mixture of 66 mg (0.179 mmol) of 2-chlorobenzenesulfonic acid 3[(N-3-aminopropoxy)-N-methylamino]methylphenyl ester dihydrochloride, as prepared in the preceding step, was treated with 66 mg (0.532 mmol) of aminoiminosulfuric acid, and 425 μ L (2.44 mmol) of diisopropylethylamine in 1 mL of N,N-dimethylformamide. The reaction mixture was stirred overnight, concentrated, and treated with 3 mL of 2 N sodium hydroxide. The reaction mixture was diluted with water, extracted into methylene chloride, dried (K_2CO_3), and concentrated. The residue was treated with 200 μ L of acetic acid and passed through a Sep-Pak silica gel column (10g) using elutions of methylene chloride/methanol/acetic acid (57.3:39.7:3) to give 27 mg of the title compound as a gum: 1H -NMR (300 MHz, DMSO- d_6) δ 8.8 (br s, 1 H), 7.77-7.90 (m, 7 H), 7.56 (dt, 1 H), 7.34 (t, 1 H), 7.22 (d, 1 H), 6.98-7.03 (m, 1 H), 2.28 (t, 2 H), 1.91 (s, 3 H), 1.76 (s, 3 H), and 1.59 (pentet, 2 H). Mass spectrum (MALDI-TOF; α -cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{18}H_{23}ClN_4O_3S$: 411.1 (M + H). Found: 411.1.

Example 57

In Vitro Inhibition of Purified Enzymes

Reagents: All buffer salts were obtained from Sigma Chemical Company (St. Louis, MO), and were of the highest purity available. The enzyme substrates, N-benzoyl-Phe-Val-Arg-*p*-nitroanilide (Sigma B7632), N-benzoyl-Ile-Glu-Gly-Arg-*p*-nitroanilide (Sigma B2291), N-*p*-tosyl-Gly-Pro-Lys-*p*-nitroanilide (Sigma T6140), and N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide (Sigma S7388) were all obtained from Sigma.

Human α -thrombin, human factor Xa, and human plasmin were obtained from Enzyme Research Laboratories (South Bend, Indiana). Bovine α -chymotrypsin and bovine trypsin were obtained from Sigma.

K_i Determinations: All assays are based on the ability of the test compound to inhibit the enzyme-catalyzed hydrolysis of a peptide *p*-nitroanilide substrate. In a typical *K_i* determination, substrate is prepared in DMSO, and diluted into an assay buffer consisting of 50 mM HEPES, 200 mM NaCl, pH 7.5. The final concentration for each of the substrates is listed below. In general, substrate concentrations are lower than the experimentally determined value for *K_m*. Test compounds are prepared as a 0.16 mg/mL solution in DMSO. Dilutions are prepared in DMSO yielding 8 final concentrations encompassing a 200-fold concentration range. Enzyme solutions are prepared at the concentrations listed below in assay buffer.

In a typical *K_i* determination, into each well of a 96 well plate is pipetted 280 μ L of substrate solution, 10 μ L of inhibitor solution, and the plate allowed to thermally equilibrate at 37°C in a Molecular Devices plate reader for >10 minutes. Reactions were initiated by the addition of a 20 μ L aliquot of enzyme, and the absorbance increase at 405 nm is recorded for 15 minutes. Data corresponding to less than 10% of the total substrate hydrolysis were used in the calculations. The ratio of the velocity (rate of the change in absorbance as a function of time) for a sample containing no inhibitor is divided by the velocity of a sample containing inhibitor, and is plotted as a function of inhibitor concentration. The data are fit to a linear regression, and the value of the slope of the line calculated. The inverse of the slope is the experimentally determined *K_i* value.

Thrombin: Thrombin activity was assessed as the ability to hydrolyze the substrate Suc-Ala-Ala-Pro-Arg-*p*NA. Substrate solutions were prepared at a concentration of 20 μ M ($20\mu\text{M} \ll K_m = 180\ \mu\text{M}$) in assay buffer. Final DMSO concentration was 0.3%. Purified human α -thrombin was diluted into assay buffer to a concentration of 450 nM. Final reagent concentrations were: [thrombin] = 0.5 nM, [Suc-Ala-Ala-Pro-Arg-*p*NA] = 20 μ M.

Factor Xa: Factor Xa activity was assessed as the ability to hydrolyze the substrate Bz-Ile-Glu-Gly-Arg-pNA. Substrate solutions were prepared at a concentration of 51 μM ($51 \mu\text{M} \ll K_m = 1.3 \text{ mM}$) in assay buffer. Final DMSO concentration was 0.3%. Purified activated human Factor Xa was diluted into assay buffer to a concentration of 300 nM. Final reagent concentrations were: [FXa] = 20 nM, [Bz-Ile-Glu-Gly-Arg-pNA] = 51 μM .

Plasmin: Plasmin activity was assessed as the ability to hydrolyze the substrate Tos-Gly-Pro-Lys-pNA. Substrate solutions were prepared at a concentration of 22 μM ($22 \mu\text{M} \ll K_m = 240 \mu\text{M}$) in assay buffer. Final DMSO concentration was 0.3%. Purified human plasmin was diluted into assay buffer to a concentration of 225 nM. Final reagent concentrations were: [plasmin] = 15 nM, [Tos-Gly-Pro-Lys-pNA] = 22 μM .

Chymotrypsin: Chymotrypsin activity was assessed as the ability to hydrolyze the substrate Suc-Ala-Ala-Pro-Phe-pNA. Substrate solutions were prepared at a concentration of 14 μM ($14 \mu\text{M} \ll K_m = 61 \mu\text{M}$) in assay buffer. Final DMSO concentration was 0.3%. Purified bovine α -chymotrypsin was diluted into assay buffer to a concentration of 45 nM. Final reagent concentrations were: [chymotrypsin] = 3 nM, [Suc-Ala-Ala-Pro-Phe-pNA] = 14 μM .

Trypsin: Trypsin activity was assessed as the ability to hydrolyze the substrate Bz-Phe-Val-Arg-pNA. Substrate solutions were prepared at a concentration of 14 μM ($14 \mu\text{M} \ll K_m = 291 \mu\text{M}$) in assay buffer. Final DMSO concentration was 0.3%. Purified bovine trypsin was diluted into assay buffer to a concentration of 150 nM. Final reagent concentrations were: [Trypsin] = 10 nM, [Bz-Phe-Val-Arg-pNA] = 14 μM .

The results obtained employing synthesized compounds are given in Table 1.

Table 1

	Product of Example Number	Enzyme	K_i (μM)
5	1	Thrombin	0.25
	3	Thrombin	0.008
	4	Factor Xa	58.1
	5	Plasmin	29.2
	6	Thrombin	0.33
10	11	Trypsin	5.3
	12	Chymotrypsin	12.6
	14	Thrombin	0.026
	17	Thrombin	0.036
	24	Thrombin	0.040
15	33	Thrombin	0.034
	38	Thrombin	0.019
	42	Thrombin	0.021
	44	Thrombin	6.9

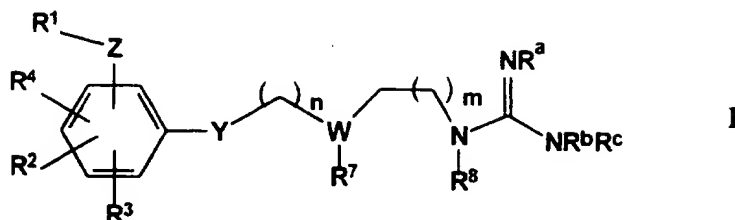
20 The results indicate that the compounds of the present invention are potent inhibitors of proteases. Compounds of the present invention inhibit a number of proteases, such as chymotrypsin, plasmin, factor Xa, thrombin and trypsin.

Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and

equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A compound having the Formula I:



or a solvate, a hydrate or a pharmaceutically acceptable salt thereof; wherein:

- 5 R^1 is one of C_{6-12} alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}C(R^yR^z)-$, $-C(R^yR^z)NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OC(R^yR^z)-$, $-C(R^yR^z)O-$, $-NR^{10}CO-$ or $-CONR^{10}-$, where

- 10 R^y and R^z are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy; and R^{10} is defined below;

- 15 R^2 , R^3 and R^4 are each independently one of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamido, $-CO_2R^x$, $-CH_2OR^x$ or $-OR^x$, or when present on adjacent carbon atoms R^2 and R^3 may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is defined as above;

- 20 R^x , in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of $-O-$, $-NR^5-$, $-S-$, $-CR^5R^9-$ or a covalent bond;

W is N or CR^{10} ;

-123-

R^7 and R^8 are each independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

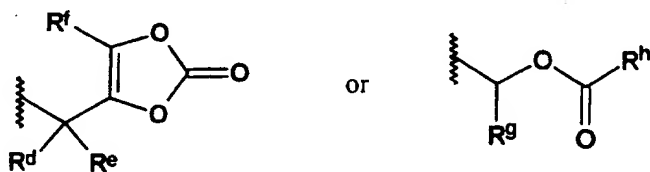
5 R^5 , in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxyalkyl;

R^9 is one of alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

10 R^{10} is hydrogen, aryl, aralkyl, alkyl, alkyloxyalkyl, wherein said alkyl or alkyloxyalkyl may be substituted by a single amino, monoalkylamino, dialkylamino, carboxy, or by one or more hydroxy groups, wherein the hydroxy groups can be further substituted by alkyl, hydroxyalkyl, alkyloxyalkyl, hydroxyalkyloxyalkyl or alkylcarbonyl groups and wherein two vicinal hydroxy groups can each be linked by an alkylidene group; or R^{10} can form the group $-E-P(O)R^{11}R^{12}$, where E is alkylene, preferably having one to 4 carbon atoms; and R^{11} and R^{12} are independently C_{1-6} alkyl groups;

15 R^a , R^b and R^c are independently hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxy-carbonyloxy, cyano or $-CO_2R^*$, where

R^* is alkyl, cycloalkyl, phenyl, benzyl.



20 where R^d and R^e are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^f is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^g is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, and R^h is aralkyl or C_{1-6} alkyl;

n is from zero to 8, with the proviso that when W is N and Y is other than $-CR^9R^{10}-$, then n is from 2 to 8; and

m is from zero to 4, provided that when (a) W is N, or (b) W is C, R⁷ and R⁸ together form $-(CH_2)_y-$ and y is 2, then m is not zero.

2. A compound of claim 1, wherein

R¹ is one of C₆₋₁₂alkyl, cycloalkyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted by one or more of hydroxy, nitro, trifluoromethyl, halogen, alkoxy, cyano, amino, monoalkylamino, dialkylamino, carboxyalkoxy, mono(carboxyalkyl)amino, di(carboxyalkyl)amino, amidino, guanidino, ditrifluoromethoxy or perfluoroethoxy, and wherein said aryl, cycloalkyl and aralkyl may further be optionally substituted by one or more alkyl moieties;

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}CH_2-$, $-CH_2NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OCH_2-$ or $-CH_2O-$;

R², R³ and R⁴ are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, $-CO_2R^x$, $-CH_2OR^x$ or $-OR^x$, or when present on adjacent carbon atoms, R² and R³ may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R⁴ is defined as above;

R^x, in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of $-O-$, $-NR^{10}-$, $-S-$, $-CR^5R^9-$ or a covalent bond;

W is N or CR¹⁰;

R^a, R^b and R^c are independently one of hydrogen, alkyl, cyano or $-CO_2R^y$, where R^y is alkyl or cycloalkyl;

R⁷ and R⁸ are each independently one of hydrogen, alkyl, aralkyl, aryl, C₂₋₁₀hydroxyalkyl or carboxyalkyl, or R⁷ and R⁸ are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

R⁹ is one of alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

-125-

R^5 and R^{10} , in each instance, are independently one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or carboxyalkyl;

n is from zero to 8, with the proviso that when W is N and Y is other than $-CR^9R^{10}-$, then n is from 2 to 8; and

5 m is from zero to 4, provided that when (a) W is N , or (b) W is C , R^7 and R^8 together form $-(CH_2)_y-$ and y is 2, then m is not zero.

3. A compound of claim 1, wherein Z is $-SO_2NR^{10}-$, $-SO_2O-$ or $-CH_2O-$.

10 4. A compound of claim 1, wherein R^1 is one of C_{4-7} cycloalkyl or C_{6-12} aryl, either of which is optionally substituted by one or more of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkoxy, C_{1-6} alkyl, amino, mono(C_{1-6})alkylamino, di(C_{1-6})alkylamino, cyano, amidino, guanidino, carboxyalkoxy, trifluoromethoxy or perfluoroethoxy.

15 5. A compound of claim 1, wherein R^1 is heteroaryl, optionally substituted by one or more of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkoxy, C_{1-6} alkyl, amino, mono(C_{1-6})alkylamino, di(C_{1-6})alkylamino, cyano, amidino, guanidino, carboxyalkoxy, trifluoromethoxy or perfluoroethoxy.

20 6. A compound of claim 1, wherein Y is one of $-O-$ or $-NR^{10}-$, and R^{10} in each instance is one of hydrogen, C_{1-6} alkyl, benzyl, phenethyl, C_{2-10} hydroxyalkyl or C_{2-7} carboxyalkyl.

7. A compound of claim 1, wherein R^a , R^b and R^c are hydrogen.

8. A compound of claim 1, wherein R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl or C_{2-7} carboxyalkyl.

-126-

9. A compound of claim 1, wherein R^7 and R^8 are taken together to form $-(CH_2)_y-$, and y is 0, 1 or 2.

10. A compound of claim 1, wherein n is from 1 to 4.

11. A compound of claim 1, wherein:

5 R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxy-carbonylamino, C_{2-6} alkoxy-carbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6}) alkoxy-carbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkyl, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy;

15 Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-C(R^yR^z)O-$ or $-OC(R^yR^z)-$, where R^y and R^z are each hydrogen;

20 R^2 , R^3 and R^4 are independently one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamido, carboxy, C_{1-4} alkoxy-carbonyl, C_{1-4} alkoxy-methyl or C_{1-4} alkoxy; or alternatively, R^2 and R^3 , when present on adjacent carbon atoms, may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is as defined above;

Y is one of $-O-$, $-S-$, $-NR^{10}-$, or a covalent bond;

25 R^6 is one of hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, mono(C_{1-4})alkylamino(C_{2-8})alkyl, di(C_{1-4})alkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

-127-

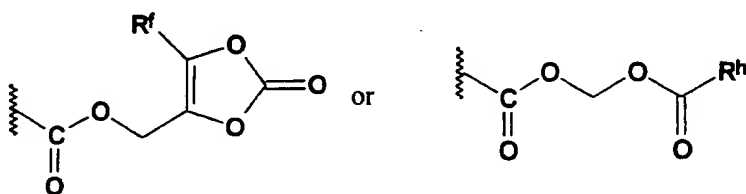
R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$ where y is zero, 1 or 2;

5 R^5 , in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

R^9 is one of C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

10 R^{10} is hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{1-6} alkyloxy(C_{1-6})alkyl, wherein said C_{1-6} alkyl or C_{1-6} alkyloxy(C_{1-6})alkyl may be substituted by a single amino, C_{1-4} monoalkylamino, di(C_{1-4})alkylamino, carboxy, or by one or more hydroxy groups, or R^{10} can form the group $-E-P(O)R^{11}R^{12}$, where E is alkylene, preferably having one to 4 carbon atoms; and R^{11} and R^{12} are independently C_{1-6} alkyl groups;

15 R^a , R^b and R^c are each one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl, benzyloxycarbonyl, cyano,



where R^h is benzyl, methyl, ethyl, isopropyl, *sec*-butyl or *t*-butyl, and

where R^f is hydrogen or C_{1-6} alkyl;

20 n is from zero to 8, with the proviso that when W is N, then n is from 2 to 8; and

m is from zero to 4, provided that when W is N, then m is not zero.

12. A compound of claim 11, wherein:

-128-

R^1 is one of phenyl or naphthyl, optionally substituted by one or two of chloro, trifluoromethyl, amino or dimethylamino;

Z is one of $-\text{SO}_2\text{O}-$, $-\text{SO}_2\text{NR}^{10}-$, $-\text{CH}_2\text{O}-$ or $-\text{OCH}_2-$;

R^2 and R^3 are each hydrogen or R^2 and R^3 may also be taken together to form $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$;

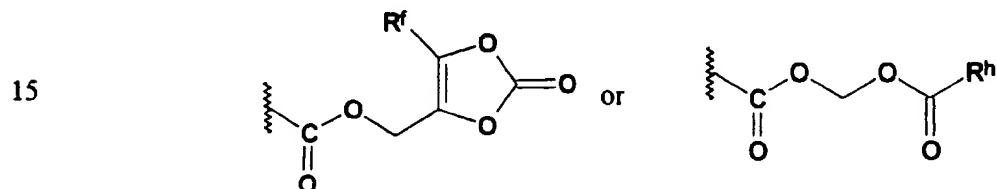
R^4 is one of hydrogen, methyl, methoxy or trifluoromethyl;

Y is one of $-\text{O}-$, $-\text{NR}^{10}-$ or a covalent bond, where R^{10} is defined below;

R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl, or R^7 and R^8 are taken together to form $-(\text{CH}_2)_y-$, where y is zero, 1 or 2;

R^{10} is independently hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

R^a , R^b and R^c are hydrogen, hydroxy,



where R^h is benzyl or *t*-butyl, and where R^f is hydrogen or methyl;

n is from zero to 4; and m is zero, 1, 2 or 3.

13. A compound of claim 1, which is one of
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]phenyl ester,
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-3-yl]methoxy]phenyl ester,
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester,

- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-3-yl]methoxy]-5-methylphenyl ester,
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-carbomethoxyphenyl ester,
- 5 3-(2-chlorobenzoyloxy)-5-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]toluene acetic acid salt,
- N-benzyl-N-[[3-(1-aminoiminomethyl)piperidin-4-ylmethylamino]phenyl]benzenesulfonamide,
- 10 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-4-benzylphenyl ester acetic acid salt,
- 1-naphthalenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
- 3-trifluoromethylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
- 15 benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
- 3-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt.
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methoxyphenyl ester,
- 20 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-4-ethoxycarbonyl-5-methylphenyl ester hydrochloride,
- 2-trifluoromethylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
- 25 3-methylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester acetic acid salt,
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-ethylphenyl ester hydrochloride,
- 2,3-dichlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride,
- 30

- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]naphthalen-1-yl ester hydrochloride,
 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-hydroxymethylphenyl ester,
 5 2-[(2-chlorobenzenesulfonyl)-[3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino]acetic acid hydrochloride,
 2-[benzenesulfonyl]-[3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl]amino]acetic acid hydrochloride,
 10 2-chloro-N-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-[trifluoromethyl]phenyl} benzenesulfonamide hydrochloride, or
 N-benzyl-N-[[3-(1-aminoiminomethyl)-piperidin-4-ylmethyl]-carboxymethyl]amino]phenyl]-2-chlorobenzenesulfonamide.
14. A compound of claim 1, which is one of:
- 15 2-chlorobenzenesulfonic acid 3-[2-[1-(aminoiminomethyl)piperazin-4-yl]ethoxy]phenyl ester diacetic acid salt, or
 2-chlorobenzenesulfonic acid 3-[2-[1-(aminoiminomethyl)piperazin-4-yl]ethoxy]-5-methylphenyl ester diacetic acid salt.
15. A compound of claim 1, which is one of:
- 20 N-methyl-N-[2-[(4-aminoiminomethylamino)butyloxy]-4-methylphenyl]-benzenesulfonamide, acetic acid salt,
 2-chlorobenzenesulfonic acid 3-[3-(aminoiminomethyl)amino]propoxy]-5-methylphenyl ester acetic acid salt,
 2-chlorobenzenesulfonic acid 3-[[4-(aminoiminomethyl)amino]butoxy]-5-methylphenyl ester acetic acid salt, or
 25 2-chlorobenzenesulfonic acid 3-[[5-(aminoiminomethyl)amino]pentoxy]-5-methylphenyl ester hydrochloride.

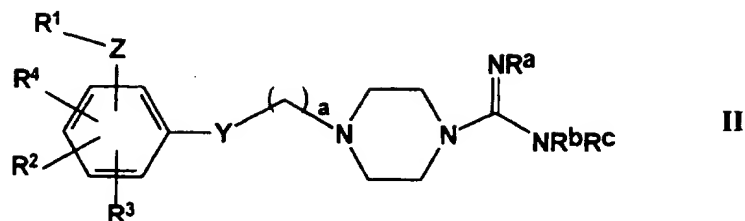
-131-

16. A compound of claim 1, which is one of:
- 3-methoxybenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 3-[(carboxy)methoxy]benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester;
- 3-hydroxybenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 3-(2'-hydroxyethoxy)benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidine-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 3-(2',3'-dihydroxypropoxy)benzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-chlorophenyl ester hydrochloride;
- 3-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 3-aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 2-methoxycarbonylbenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 4-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 4-aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 2-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 2-aminobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

- 2-chloro-3-nitrobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;
- 3-amino-2-chlorobenzenesulfonic acid 3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester dihydrochloride;
- 5 2-chlorobenzenesulfonic acid 5-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-2-(ethoxycarbonyl)-3-methylphenyl ester hydrochloride;
- 2-chlorobenzenesulfonic acid 1-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester acetic acid salt;
- 3-(2-chlorobenzyloxy)-1-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]benzene acetic acid salt;
- 10 6-((2-chlorobenzenesulfonyl)-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl}amino)hexanoic acid methyl ester hydrochloride;
- 6-((2-chlorobenzenesulfonyl)-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl}amino)hexanoic acid hydrochloride;
- 15 6-((2-chlorobenzenesulfonyl)-{3-[[1-(aminoiminomethyl)piperidin-4-yl]methoxy]-5-(trifluoromethyl)phenyl}amino)hexanoic acid;
- N-(2-propyl)-N-{[3-(1-aminoiminomethyl)piperidin-4-ylmethoxy]-5-trifluoromethyl}phenyl-2-chlorobenzenesulfonamide hydrochloride;
- 20 2-chlorobenzenesulfonic acid 3-[[1-(N-methoxycarbonyl-aminoiminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester;
- 2-chloro-3-nitrobenzenesulfonic acid 3-[[1-((N-methoxycarbonylamino)-N-methoxy-carbonyliminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester;
- 25 2-chloro-3-nitrobenzenesulfonic acid 3-[[1-((N,N-di(methoxycarbonyl)-amino)-N-methoxycarbonyliminomethyl)piperidin-4-yl]methoxy]-5-methylphenyl ester; and
- 2-chlorobenzenesulfonic acid 3-{N-[[3-(aminoiminomethyl)amino]propyl]-N-(methyl)aminomethyl}phenyl ester acetic acid salt.

-133-

17. A compound of claim 1, having the formula:

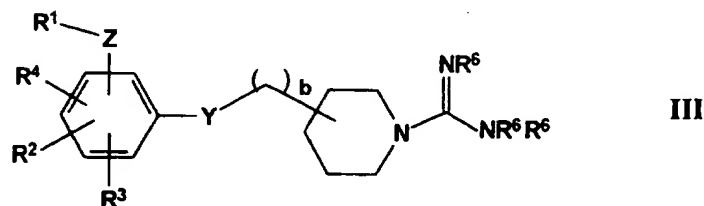


or a solvate, a hydrate or a pharmaceutically acceptable salt thereof; wherein:

R^1 , Z, R^2 , R^3 , R^4 , Y, R^a , R^b and R^c are defined in claim 1; and

5 a is from 1 to 8, provided that when Y is other than $-CR^5R^9-$, then a is from 2 to 8.

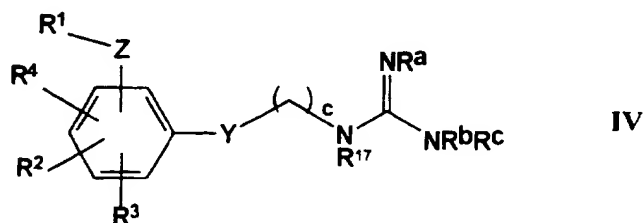
18. A compound of claim 1, having the formula:



or a solvate, a hydrate or a pharmaceutically acceptable salt thereof; wherein:

10 R^1 , Z, R^2 , R^3 , R^4 , Y, R^a , R^b and R^c are defined in claim 1; and
b is from 1 to 8.

19. A compound of claim 1, having the formula:



-134-

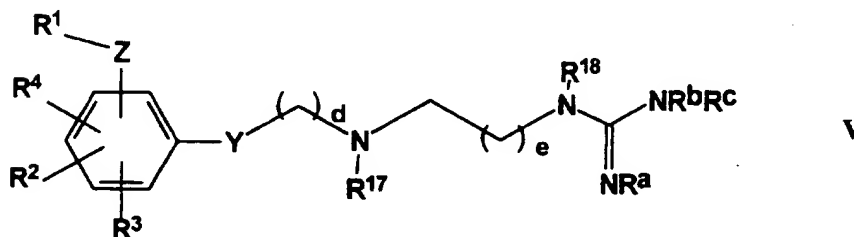
or solvates, hydrates or pharmaceutically acceptable salts thereof; wherein:

R^1 , Z, R^2 , R^3 , R^4 , Y, R^a , R^b and R^c are defined in claim 1;

R^{17} is one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or carboxyalkyl; and

5 c is from 1 to 14, provided that when Y is other than $-CR^5R^9-$, then c is from 2-14.

20. A compound of claim 1, having the formula:



or solvates, hydrates or pharmaceutically acceptable salts thereof; wherein:

10 R^1 , Z, R^2 , R^3 , R^4 , Y, R^a , R^b and R^c are defined in claim 1;

R^{17} and R^{18} are each independently one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or carboxyalkyl;

d is from 1 to 8; with the proviso that when Y is other than $-CR^5R^9-$ then d is from 2 to 8; and

15 e is from 1 to 4.

21. A compound of any of claims 17-20, wherein:

20 R^1 is one of C_{6-12} alkyl, cycloalkyl aryl, aralkyl or heteroaryl, any of which may be optionally substituted by one or more of hydroxy, nitro, trifluoromethyl, halogen, alkoxy, cyano, amino, monoalkylamino, dialkylamino, carboxyalkoxy, mono(carboxyalkyl)amino, di(carboxyalkyl)amino, amidino, guanidino, ditrifluoromethoxy or perfluoroethoxy, and wherein said aryl, cycloalkyl and aralkyl may further be optionally substituted by one or more alkyl moieties;

-135-

Z is one of $-\text{NR}^{10}\text{SO}_2-$, $-\text{SO}_2\text{NR}^{10}-$, $-\text{NR}^{10}\text{CH}_2-$, $-\text{CH}_2\text{NR}^{10}-$, $-\text{OSO}_2-$, $-\text{SO}_2\text{O}-$, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$;

R^2 , R^3 and R^4 are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, $-\text{CO}_2\text{R}^x$, $-\text{CH}_2\text{OR}^x$ or $-\text{OR}^x$, or when present on adjacent carbon atoms, R^2 and R^3 may also be taken together to form one of $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-(\text{CH}_2)_q-$, where q is from 2 to 6, and R^4 is defined as above;

R^x , in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of $-\text{O}-$, $-\text{NR}^{10}-$, $-\text{S}-$, $-\text{CR}^5\text{R}^9-$ or a covalent bond;

R^9 is one of alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

R^5 and R^{10} , in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or carboxyalkyl; and

R^a , R^b and R^c are independently hydrogen, alkyl, cyano or $-\text{CO}_2\text{R}^y$, where R^y is alkyl or cycloalkyl;

22. A compound of any of claims 17-20, wherein:

R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6}) alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkyl, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy;

Z is one of $-\text{SO}_2\text{O}-$, $-\text{SO}_2\text{NR}^{10}-$, $-\text{C}(\text{R}^y\text{R}^z)\text{O}-$ or $-\text{OC}(\text{R}^y\text{R}^z)-$, where R^y and R^z are each hydrogen;

R^2 , R^3 and R^4 are independently one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamido, carboxy, C_{1-4} alkoxy carbonyl, C_{1-4} alkoxy methyl or C_{1-4} alkoxy; or alternatively, R^2 and R^3 , when present on adjacent carbon atoms, may also be taken together to form one of $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-(\text{CH}_2)_q-$, where q is from 2 to 6, and R^4 is as defined above;

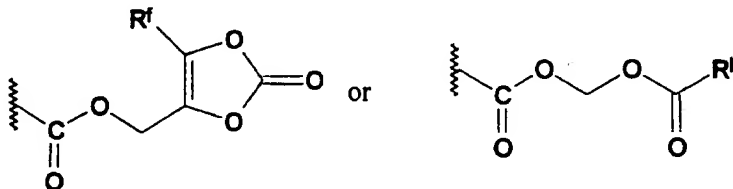
Y is one of $-\text{O}-$, $-\text{S}-$, $-\text{NR}^{10}-$, or a covalent bond;

R^5 , in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

R^9 is one of C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^{10} is hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{1-6} alkyloxy(C_{1-6})alkyl, wherein said C_{1-6} alkyl or C_{1-6} alkyloxy(C_{1-6})alkyl may be substituted by a single amino, C_{1-4} monoalkylamino, di(C_{1-4})alkylamino, carboxy, or by one or more hydroxy groups, or R^{10} can form the group $-\text{E}-\text{P}(\text{O})\text{R}^{11}\text{R}^{12}$, where E is alkylene, preferably having one to 4 carbon atoms; and R^{11} and R^{12} are independently C_{1-6} alkyl groups; and

R^a , R^b and R^c are each one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl, benzyloxycarbonyl, cyano,



where R^h is benzyl, methyl, ethyl, isopropyl, *sec*-butyl or *t*-butyl, and where R^f is hydrogen or C_{1-6} alkyl.

-137-

23. A compound of claim 22, wherein:

R^1 is one of phenyl or naphthyl, optionally substituted by one or two of chloro, trifluoromethyl, amino or dimethylamino;

Z is one of $-\text{SO}_2\text{O}-$, $-\text{SO}_2\text{NR}^{10}-$, $-\text{CH}_2\text{O}-$ or $-\text{OCH}_2-$;

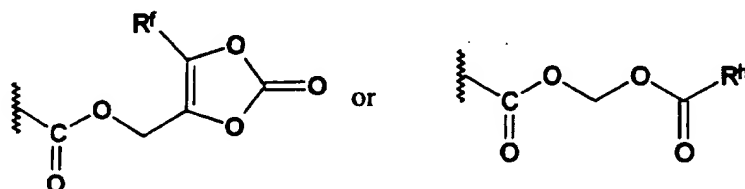
R^2 and R^3 are each hydrogen or R^2 and R^3 may also be taken together to form $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$;

R^4 is one of hydrogen, methyl, methoxy or trifluoromethyl;

Y is one of $-\text{O}-$, $-\text{NR}^{10}-$ or a covalent bond, where R^{10} is defined below;

R^{10} is independently hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl; and

R^a , R^b and R^c are hydrogen, hydroxy,



where R^h is benzyl or *t*-butyl, and where R^f is hydrogen or methyl.

24. A compound of any of claims 17-20, wherein Z is one of $-\text{SO}_2\text{NR}^{10}-$, $-\text{SO}_2\text{O}-$ or $-\text{CH}_2\text{O}-$.

25. A compound of any of claims 17-20, wherein R^1 is one of C_{4-7} cycloalkyl or C_{6-12} aryl, either of which is optionally substituted by one or more of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkoxy, C_{1-6} alkyl, amino, mono(C_{1-6})alkylamino, di(C_{1-6})alkylamino, amidino, guanidino, cyano, carboxyalkyloxy, trifluoromethoxy or perfluoroethoxy.

-138-

26. A compound of any of claims 17-20, wherein R¹ is heteroaryl, optionally substituted by one or more of hydroxy, nitro, trifluoromethyl, halogen, C₁₋₆alkoxy, C₁₋₆alkyl, amino, mono(C₁₋₆)alkylamino, di(C₁₋₆)alkylamino, amidino, guanidino, cyano, carboxyalkyloxy, trifluoromethoxy or perfluoroethoxy.
- 5 27. A compound of any of claims 17-20, wherein Y is one of -O- or -NR¹⁰-, and R¹⁰ in each instance is one of hydrogen, C₁₋₆alkyl, benzyl, phenethyl, C₂₋₁₀hydroxyalkyl or C₂₋₇carboxyalkyl.
28. A compound of claim 20, wherein d is 2, 3 or 4, and e is 1 or 2.
- 10 29. A compound of any of claims 17-20, wherein R^a, R^b and R^c are hydrogen.
30. A pharmaceutical composition for inhibiting proteolysis in a mammal, comprising an amount of a compound of claim 1 effective to inhibit proteolysis, and a pharmaceutically acceptable carrier or diluent.
- 15 31. A pharmaceutical composition for inhibiting proteolysis in a mammal, comprising an amount of a compound of claim 11 effective to inhibit proteolysis, and a pharmaceutically acceptable carrier or diluent.
32. A pharmaceutical composition for inhibiting proteolysis in a mammal, comprising an amount of a compound of claim 12 effective to inhibit proteolysis, and a pharmaceutically acceptable carrier or diluent.
- 20 33. A pharmaceutical composition for inhibiting proteolysis in a mammal, comprising an amount of a compound of any one of claims 13-16 effective to inhibit proteolysis, and a pharmaceutically acceptable carrier or diluent.

34. A pharmaceutical composition for inhibiting proteolysis in a mammal, comprising an amount of a compound of any one of claims 17-20 effective to inhibit proteolysis, and a pharmaceutically acceptable carrier or diluent.

5 35. A method of inhibiting proteolysis in a mammal, comprising administering to the mammal a composition of claim 30.

36. A method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation in a mammal, comprising administering to the mammal a composition of claim 30.

10 37. A method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma, comprising administering to the mammal a composition of claim 30.

38. A method of inhibiting proteolysis in a mammal, comprising administering to the mammal a composition of claim 31.

15 39. A method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation in a mammal, comprising administering to the mammal a composition of claim 31.

20 40. A method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma, comprising administering to the mammal a composition of claim 31.

41. A method of inhibiting proteolysis in a mammal, comprising administering to the mammal a composition of claim 32.

-140-

42. A method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation in a mammal, comprising administering to the mammal a composition of claim 32.

5 43. A method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma, comprising administering to the mammal a composition of claim 32.

44. A method of inhibiting proteolysis in a mammal, comprising administering to the mammal a composition of claim 33.

10 45. A method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation in a mammal, comprising administering to the mammal a composition of claim 33.

46. A method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma, comprising administering to the mammal a composition of claim 33.

15 47. A method of inhibiting proteolysis in a mammal, comprising administering to the mammal a composition of claim 34.

48. A method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation in a mammal, comprising administering to the mammal a composition of claim 34.

20 49. A method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma, comprising administering to the mammal a composition of claim 34.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15609

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/255, 317, 331, 603, 604, 634, 822; 564/237; 546/229, 230, 231; 544/398, 399, 400, 402

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,577,432 A (HELSLEY) 04 May 1971.	1-49
A	US 4,433,152 A (MURAMATSU ET AL.) 21 February 1984.	1-49
A	US 5,260,307 A (ACKERMAN ET AL.) 09 November 1993.	1-49
A	JP 50-140474 A (TAKAHESI ET AL.) 11 November 1975, see abstract.	1-49
A	RYZNERSKI, Z., et al. Synthesis and Pharmacological Properties of Phenoxyethylpiperazine Derivatives Pol. J. Pharmacol. Pharm. 1989, Vol. 41, pages 191-199.	1-49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

09 JANUARY 1997

Date of mailing of the international search report

03 FEB 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

RAYMOND COVINGTON

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15609

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15609

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

A61K 31/18, 31/155, 31/445, 31/495; C07C 277/00, 279/00, 279/12; C07D 211/26, 211/60, 241/04, 295/00

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

514/255, 317, 331, 603, 604, 634, 822; 564/237; 546/229, 230, 231; 544/398, 399, 400, 402

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1.

Group I, claims 1-35, 38, 41, 44 and 47 drawn to compounds and method of inhibiting proteolysis.

Group II, claims 37, 39, 42, 45 and 48 drawn to a method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation.

Group III, claims 37, 40, 43, 46 and 49 drawn to a method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma.

The inventions listed as Groups I, II and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: they have different functions and effects. For example, group I can be used in purification and isolation processes, group II is used to treat inflammation states and group III is used to inhibit thrombin production in circulatory state.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

(a) compounds where R^7/R^8 are independent, all other variables being the same; (b) compounds where R^7/R^8 form a ring where W is nitrogen, all other variables being the same; (c) compounds where R^7/R^8 form a ring where W is hydrogen, all other variables being the same.